Use of routine program data & evaluation data to maximize the impact of prevention of mother to child transmission of HIV (PMTCT) programs in Nigeria & Malawi

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Abstract

Background

Great progress has been made in preventing mother to child transmission of HIV (PMTCT), however programmatic and operational challenges remain. Utilizing routinely collected PMTCT program data to refine epidemiologic estimates and describe facility-level factors that influence maternal and infant outcomes is critical to addressing these challenges.

Objectives

In this dissertation, we (1) compared HIV positivity rates from PMTCT data to HIV prevalence estimates from antenatal care sentinel surveillance (ANC-SS) in Nigeria (2014-2015); (2) estimated local government area (LGA) HIV prevalence in Nigeria using PMTCT data (2015); and (3) determined the association between facility-level factors and maternal and infant HIV outcomes in Malawi's national PMTCT program (2015-2016).

Methods

We used exploratory analyses and linear regression to quantify the difference between site- and state-level HIV prevalence estimates using PMTCT testing data (n=2.2 million) compared to ANC-SS data (n=36,431). We used Empirical Bayes approaches and multilevel modeling to generate LGA HIV prevalence estimates using PMTCT data. Finally, we used multilevel logistic regression to measure the association between

facility level factors and individual-level maternal and infant outcomes using enrollment data from the National Evaluation of Malawi's PMTCT Program (NEMAPP) (n=3,489 mother baby pairs, 54 facilities), facility staffing data, and PMTCT program data.

Results

ANC-SS-based HIV prevalence estimates at the facility and state levels differ significantly from estimates generated using routine PMTCT program data in Nigeria. Many states (62%) in Nigeria have statistically significant within-state variation in LGA-level HIV prevalence. In Malawi, mothers who sought care at public facilities (vs faith-based) were significantly more likely to have infants testing positive for HIV at 6 weeks postpartum and were less likely to be on ART during pregnancy. Mothers seeking care at sites with a high provider-to-patient ratio, a high proportion of patients newly diagnosed with HIV, and who traveled > 2 hours to reach the facility were significantly more likely to be on ART during pregnancy.

Conclusions

This dissertation demonstrates how routinely collected program data can be used to generate granular descriptive epidemiologic data, and to complement evaluation, survey, and surveillance data in multilevel analyses, allowing leaders to diagnose issues and intervene accordingly to improve PMTCT programs.

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Abbreviations & Acronyms

AIDS	Acquired Immunodeficiency Syndrome
ANC	Antenatal care
ANC-SS	Antenatal care Sentinel Surveillance
ARVs	Antiretroviral medication
ART	Antiretroviral therapy
DNA PCR	DNA (Deoxyribonucleic Acid) Polymerase Chain Reaction: diagnostic method used for early diagnosis of HIV in infants
EID	Early infant diagnosis
HEI	HIV-exposed infant
HIV	Human Immunodeficiency Virus
LGA	Local government area; administrative unit in Nigeria similar to a district
MOH	Ministry of Health
MTCT	Mother-to-child transmission of HIV
NEMAPP	National Evaluation of Malawi's PMTCT Program
Option B+	Lifelong antiretroviral therapy provided to pregnant or lactating mothers to protect maternal health and prevent mother-to-child transmission of HIV
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PMTCT	Prevention of mother-to-child transmission of HIV
PNC	Postnatal care

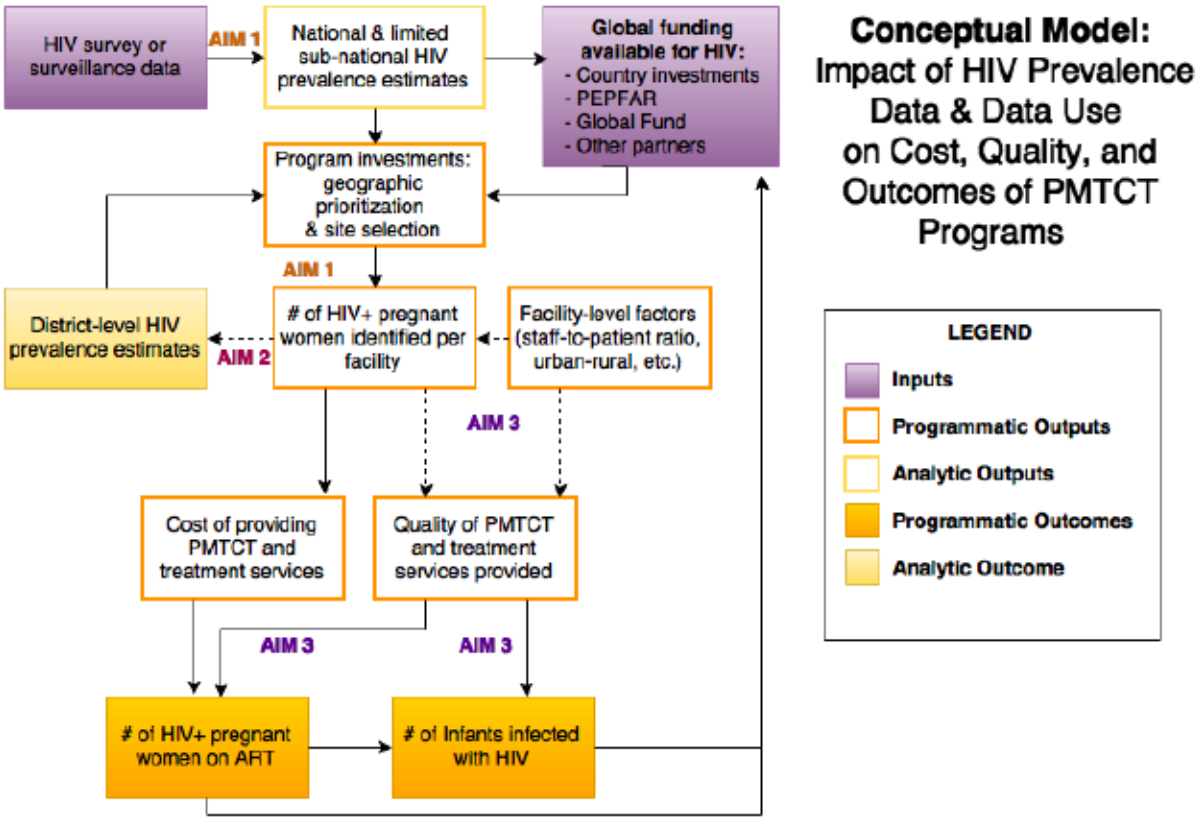
Chapter 1 : Introduction

Organization

This dissertation is organized into five chapters. Chapter 1 provides an introduction to the topic, presenting the conceptual model informing the dissertation, and an overview of the three specific aims. Chapter 2 provides background information on prevention of mother-to-child transmission of HIV (PMTCT) globally, and in the two countries highlighted in the analyses: Nigeria and Malawi. Chapter 3 presents the analysis comprising aims 1 and 2, and is focused on (1) comparing HIV prevalence estimates generated using ANC sentinel surveillance data versus estimates based on routinely collected PMTCT program data, and (2) use of PMTCT program data to estimate HIV prevalence at the local government area (LGA) level. Chapter 4 presents the aim 3 analysis, assessing the association between facility-level factors and maternal and infant HIV outcomes in Malawi's national PMTCT program. Chapter 5 provides a summary of the dissertation as a whole and presents conclusions and implications of the findings for research and for public health practice.

Conceptual Model

Figure 1-1: Conceptual Model showing the impact of HIV prevalence data, data use, and health facility-level factors on the cost, quality, and outcomes of PMTCT programs



The conceptual model presented in Figure 1 1 reflects the theoretical basis of this dissertation. HIV survey or surveillance data are used to generate national and state-level HIV prevalence estimates in Nigeria. These HIV prevalence estimates drive both the availability of global HIV/AIDS resources, and the geographic prioritization of HIV investments, at global, national, and sub-national levels. Health facilities (sites) are prioritized to receive funding for PMTCT programming based on where the burden of disease is thought to be greatest. The Aim 1 analysis compares site-level positivity rates among pregnant women tested for HIV through antenatal care sentinel surveillance

(ANC-SS) to positivity rates from routinely collected PMTCT program data in the same facilities. The Aim 2 analysis uses site-level PMTCT program data on the number of pregnant women tested for HIV and the number testing positive to estimate local government area (LGA)-level HIV prevalence estimates in Nigeria. These LGA-level estimates can be used to refine PMTCT site selection, thus maximizing the number of HIV positive pregnant women identified with limited resources, and decreasing the cost of service provision while (we hypothesize) improving the quality of PMTCT services. This should ultimately increase the number of pregnant women living with HIV who receive antiretroviral therapy (ART) during pregnancy, while decreasing the number of HIV-exposed infants who are infected with HIV. The Aim 3 analysis explores the association between facility-level factors and individual maternal and infant HIV outcomes.

Specific Aims

The specific aims of this dissertation are as follows:

1. To evaluate the difference between state and facility-level HIV prevalence measured through routine PMTCT program data at PEPFAR-supported sites in fiscal year 2015 compared to HIV prevalence measured at the same facilities through ANC sentinel surveillance in Nigeria in 2014

2. To estimate local government area (LGA)-level HIV prevalence among pregnant women attending antenatal care services (ANC) in PEPFAR-supported facilities in Nigeria in fiscal year 2015

3. To determine the association between health facility-level factors and maternal and infant HIV outcomes in Malawi's national PMTCT program in 2015-2016

Chapter 2 : Background

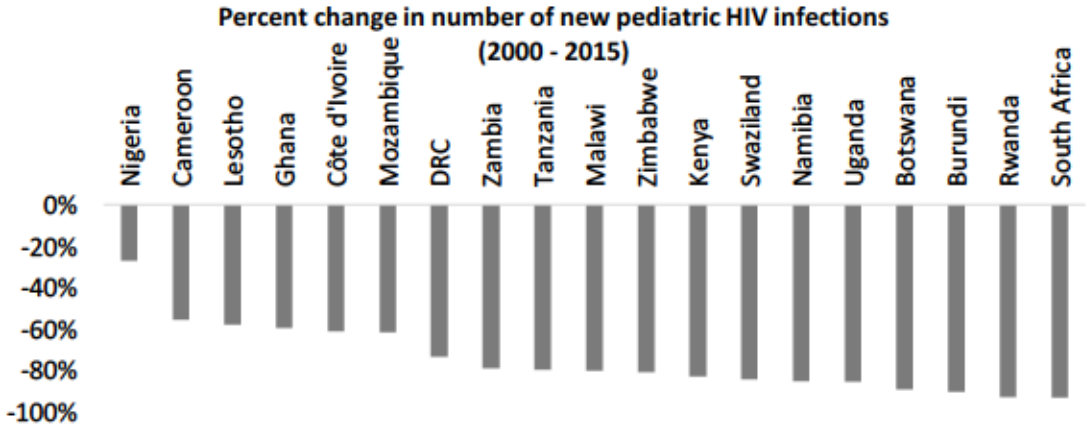
Brief overview of PMTCT globally

In 2015, there were 1.8 million children living with HIV globally, and over 150,000 infants were newly infected with HIV.[1] Studies have shown that HIV-positive pregnant women have up to a 45% chance of passing HIV to their infant during pregnancy, delivery, or breastfeeding in the absence of antiretroviral medication (ARVs).[2] ARVs administered during pregnancy and breastfeeding can reduce the vertical transmission to less than 5%.[2] HIV positive mothers not on antiretroviral therapy are eight times more likely to die in childbirth than HIV negative mothers[3,4] and if untreated, 50% of HIV-infected infants will die before their second birthday.[5]

UNAIDS estimates that 1.6 million new pediatric HIV infections have been averted due to the use of antiretroviral medications administered through PMTCT programs since 2000.[6] Due to the scale-up of PMTCT programs, the continued introduction of better antiretroviral regimens for mothers, and finally, the move towards universal eligibility for lifelong antiretroviral therapy for all pregnant and breastfeeding women, the annual number of new infant HIV infections has declined by 70% since the peak of the epidemic in 2000.[7] Additionally, universal eligibility for treatment and the use of better ARV regimens has resulted in a marked decline in maternal mortality, with an estimated 43% reduction in AIDS-related deaths among women of childbearing age between 2009 and 2015.[8]

The tremendous progress made in reducing mother-to-child transmission and keeping mothers living with HIV alive and healthy has not been equal everywhere, and a number of challenges remain. Figure 2 1 shows the geographic disparity in the reduction of new HIV infections among infants across the highest burden countries since the peak of the HIV/AIDS epidemic. The number of new HIV infections among women of childbearing age remains high: 4.5 million women were infected between 2009 and 2015,[8] leading to an estimated 18.7 million women of childbearing age living with HIV.[6] Each of these women who decide to have children will require PMTCT services to protect their health and that of their infants. Finally, timely access to early infant diagnosis and pediatric treatment for infants testing positive for HIV continues to lag in many countries. In 2015, just 51% of the 1.2 million HIV-exposed infants in high burden countries were tested for HIV by 2 months of age, and approximately 51% of children living with HIV were receiving antiretroviral therapy.[8]

Figure 2-1 : Reduction in new pediatric HIV infections; high burden countries, 2000-2015



Source: UNAIDS, AIDS Info Online Database, 2016

Brief overview of HIV/AIDS and PMTCT in Nigeria

With 3.5 million people living with HIV in 2015, Nigeria is second only to South Africa in terms of the absolute size of its epidemic. Due to low coverage of HIV testing and treatment services, 180,000 people die of AIDS-related causes each year in Nigeria - more than in any other country.[1] However, unlike most high burden countries, Nigeria's HIV prevalence is low, estimated at 3.1% among adults.[1] Scaling up HIV/AIDS services in low prevalence but large scale epidemics poses unique challenges. In Nigeria, HIV/AIDS programming competes with many other health programs which may directly affect more Nigerians. As in many low prevalence countries, HIV/AIDS is treated as a specialty rather than being integrated into standard medical and nursing curricula and healthcare delivery systems.[9] As a result, healthcare providers who rarely encounter people living with HIV may be less familiar with treatment options than providers operating in high prevalence settings. Stigma against people living with HIV has been shown to be higher in low prevalence settings, and where ART coverage is low,[10] which can further complicate successful scale-up of prevention and treatment services.

In 2015, nearly one third of all new pediatric infections occurred in Nigeria, where just 29% of mothers living with HIV have access to lifesaving antiretroviral therapy for their own health and to prevent vertical transmission of the virus to their infants.[8] Nigeria faces a number of related challenges that contribute to these statistics. The total fertility rate is 6, and an estimated 9.4 million pregnancies occur each year.[11] Uptake of

antenatal care (ANC) services is generally low (61% of women attend at least one ANC visit),[12,13] but varies tremendously by state, from a low of 18% to a high of 98%.[13] Approximately 15% of women have access to and use modern contraceptives for family planning, and 35% of all births in Nigeria occur in the company of a skilled birth attendant.[12] At the national level, UNFPA estimates that human resources for health, including nurses, midwifes, and clinicians exist in adequate numbers to meet 97% of Nigeria's maternal and neonatal healthcare needs.[11] However, despite the plentiful supply of human resources for health in Nigeria, their distribution across geopolitical zones and states varies considerably,[13] and women in rural areas are approximately four times as likely as women living in urban areas to give birth without a skilled birth attendant.[11]

Overview of HIV/AIDS and PMTCT in Malawi

In 2015, Malawi's adult HIV prevalence was 9.1% and an estimated 980,000 people were living with HIV, including 84,000 children.[1] Antiretroviral therapy (ART) coverage is moderate, at 61%, and approximately 27,000 AIDS-related deaths occurred in 2015.[1] The number of new pediatric HIV infections was 4,800 in 2015, which represents a remarkable 71% reduction since 2009.[8] In the same time period, Malawi also achieved a 34% reduction in the number of new HIV infections among women of childbearing age.[8] In 2015, approximately 80% of pregnant and breastfeeding mothers were on antiretroviral therapy for their own health and for PMTCT (compared to just 21% in 2009).[8] Despite limitations in the healthcare system (UNFPA estimates that just 27% of

Malawi's human resource needs are met for maternal and neonatal healthcare),[11] Malawi has high ANC attendance: 96% of women attend at least one ANC visit, and 87% of Malawian mothers give birth in the presence of a skilled birth attendant.[12]

Malawi was the first country in Sub-Saharan Africa to offer lifelong ART to all pregnant and breastfeeding women, regardless of disease progression. Much of Malawi's recent success in improving maternal and infant HIV outcomes are credited to the development and scale-up of this approach to PMTCT, called "Option B+". Malawi developed the Option B+ approach in response to the 2010 World Health Organization PMTCT guidelines, which relied heavily on use of CD4 cell count analysis to determine maternal eligibility for antiretroviral treatment vs prophylactic regimens. Within the first year of implementation, Option B+ led to a 748% increase in the number of pregnant and breastfeeding women initiating antiretroviral therapy each quarter.[14] In addition to removing the barrier of obtaining maternal CD4 cell count, Option B+ offered several other operational simplifications that have contributed to its successful implementation. A new task sharing policy allowed Malawi's nurses – in addition to doctors - to prescribe and initiate ART. Malawi procured a fixed dose combination for their first line treatment regimen, meaning women had to take just one pill, once daily. And the public health approach of "lifelong treatment for all pregnant and breastfeeding women" was much simpler to communicate than previous iterations of complex clinical guidelines.

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Chapter 3 : Comparing state and facility-level HIV prevalence estimates from antenatal care sentinel surveillance (ANC-SS) data and routine PMTCT program data and generating local (LGA-level) HIV prevalence estimates in Nigeria

ABSTRACT

Background

Approximately 71% of women living with HIV in Nigeria lack access to lifesaving prevention of mother-to-child transmission of HIV (PMTCT) services.[1] Resources are inadequate to support universal coverage for PMTCT, so understanding the distribution of HIV in order to prioritize local government areas (LGAs) within high burden states is critical. Currently, HIV prevalence is only estimated at the state level. The objectives of this study are: (1) to compare facility- and state-level HIV prevalence estimates based on routine PMTCT program data to estimates based on antenatal care sentinel surveillance (ANC-SS) in 2014; and (2) to estimate LGA-level HIV prevalence among pregnant women attending ANC at PMTCT sites in Nigeria in 2015.

Methods

We compared facility-level HIV prevalence estimates (n=95 facilities) from ANC-SS in 2014 and from routine PMTCT program data in 2015, characterizing the differences between estimates from these two data sources. Multilevel logistic regression models were used to extrapolate routine facility-aggregated HIV testing data from 5,662 health

facilities offering PMTCT services (n=2.2 million pregnant women) to estimate LGA-level HIV prevalence.

Results

Significant differences were found between HIV prevalence estimates generated from ANC-SS compared to PMTCT data. Although the magnitude of difference at the facility level was small on average (mean difference: 0.1%; 95% CI: [-0.7%, 0.9%]), the standard deviation was large (3.8%), and the range of absolute differences was wide [-13. 2%, 23.2%]. State-level HIV prevalence estimates were systematically higher when generated from ANC-SS data compared to PMTCT data (mean difference: 1.8%; 95% CI: [1.3%, 2.3%]). The modeled LGA-level HIV prevalence estimates document statistically significant within-state variation in LGA-level HIV prevalence in 62% of states in Nigeria.

Conclusions

Systematic differences were identified between HIV prevalence estimates from ANC-SS compared to PMTCT data at the state level, and large differences at the facility level do not appear to adhere to a discernable pattern. ANC-SS sites likely represent a biased sample of pregnant women attending ANC. PMTCT data from all available sites should be used for HIV prevalence estimation in Nigeria. The LGA prevalence estimates from this analysis demonstrate how routinely collected program data can produce the granular descriptive epidemiologic data needed for programmatic decision-making.

BACKGROUND & INTRODUCTION

In 2015, over 150,000 infants globally were infected with HIV; nearly one third of these infants were born in Nigeria.[1] UNAIDS estimates that 71% of women living with HIV in Nigeria lack access to lifesaving prevention of mother to child transmission of HIV (PMTCT) services.[2] With no intervention, HIV-positive pregnant women have up to a 45% chance of passing the virus to their infant during pregnancy, delivery, or breastfeeding.[3] Antiretroviral medication administered during pregnancy and breastfeeding can reduce the risk of mother-to-child transmission to less than 5%.[3] Without antiretroviral therapy, HIV positive mothers are eight times more likely to die in childbirth than HIV negative mothers[4,5] and without treatment, half of infants infected with HIV will die before age two.[6]

The Federal Republic of Nigeria has a federal government system with 36 states plus the federally administered capital territory of Abuja. Each state is subdivided into between 8 and 44 districts, called local government areas (LGAs).[7] Nigeria has more than 34,000 public and private health facilities.[8] Existing HIV/AIDS resources are inadequate to support scale-up of PMTCT services to every health facility; thus, in the context of limited resources for HIV/AIDS programming in Nigeria, prioritizing the LGAs with the highest burden of HIV is necessary.

The U.S. President's Emergency Plan for AIDS Relief (PEPFAR) represents the largest investment ever made towards combatting a single disease and is considered one of the

most significant and successful global health initiatives ever undertaken.[9] In 2015, PEPFAR funded an estimated 80% of PMTCT services in high burden countries,[10,11] including over 90% of PMTCT services in Nigeria.[1,12]

Identifying & Addressing Gaps in Existing Epidemiologic Data in Nigeria

There are several important gaps in available epidemiologic data for HIV in Nigeria: (1) at the state level, there are published HIV prevalence estimates but these vary substantially across data sources and years; and (2) at the LGA level, there are no reliable published HIV prevalence estimates. Granular descriptive epidemiologic data characterizing the burden of HIV in Nigeria at the local (LGA) level are needed for programmatic planning.

We begin to address these gaps in epidemiologic data by using routinely collected HIV testing from PEPFAR-supported PMTCT sites in Nigeria in fiscal year 2015 (PMTCT data) and published ANC sentinel surveillance (ANC-SS) data from Nigeria in 2014 for the following two objectives: (1) to evaluate the difference between facility-level and state-level HIV prevalence measured through routine PMTCT program data at PEPFAR-supported sites in fiscal year 2015 compared to HIV prevalence measured at the same facilities through ANC sentinel surveillance in Nigeria in 2014; and (2) to estimate local government area (LGA)-level HIV prevalence among pregnant women attending antenatal care services (ANC) in PEPFAR-supported facilities in Nigeria in fiscal year 2015.

We hypothesize that (1) on average HIV prevalence measured through ANC sentinel surveillance will be significantly higher than HIV prevalence measured through routine PMTCT program data; and (2) we hypothesize that there will be significant within-state variation in LGA-level HIV prevalence among pregnant women attending ANC.

Available state-level HIV prevalence estimates in Nigeria are based on population-representative surveys or antenatal care sentinel surveillance data. Population-representative surveys are expensive to conduct, and only occur periodically. In Nigeria, there are large discrepancies between state HIV prevalence estimates between surveys.[13,14] The scientific literature indicates that HIV prevalence should be relatively stable over a two-year period within a given geographic area in the absence of big spikes or drops in HIV incidence or AIDS deaths,[15] thus the magnitude of changes in estimated state HIV prevalence in Nigeria suggests that these existing state-level HIV prevalence estimates are unreliable. The most recently published sub-national HIV prevalence estimates are based on ANC Sentinel Surveillance data from 2010 and 2014, and a national population-representative survey (National HIV/AIDS and Reproductive Health Survey (NARHS)), published in 2012. Table 3-1 summarizes the population tested for HIV, the sample size, and the methodology for data collection for these recent surveys and surveillance reports, as well as for routinely-collected PMTCT program data from PEPFAR-supported sites.

Table 3-1: Description of source data for recent state-level HIV prevalence estimates in Nigeria

Source of HIV prevalence data	Date published	Population	Sample size	Methodology
ANC Sentinel Surveillance	2010	Pregnant women attending ANC	160 ANC sites; n=36,427 tested	Unlinked anonymous testing; samples collected at facilities and tested at state labs
NARHS survey	2012	Men and women	31,235 survey participants; n= 23,582 tested	Household survey with opt-out HIV testing; 76% uptake of HIV test
ANC Sentinel Surveillance	2014	Pregnant women attending ANC	160 ANC sites; n=36,431 tested	Unlinked anonymous testing; samples collected at facilities and tested at state labs
Routine data from PEPFAR-supported PMTCT program	2015 (annually)	Pregnant women attending ANC	5,662 ANC sites; n=2,237,055 tested	Provider-initiated opt-out testing; samples collected and tested at facilities; routine data collection

The state-level HIV prevalence estimates generated using these four sources of HIV testing data vary significantly. See Figure 3 1, Figure 3 2, Figure 3 3, and Figure 3 4.

Figure 3-1: State HIV Prevalence from ANC Sentinel Surveillance in 2010, Nigeria

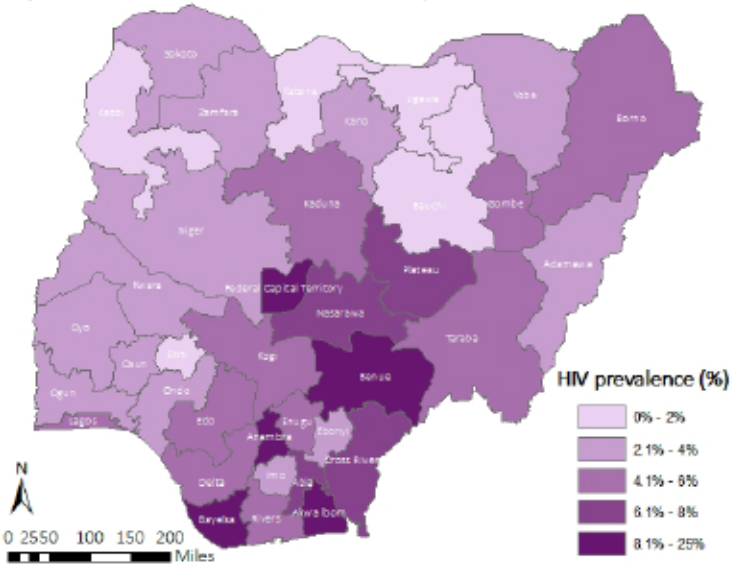


Figure 3-2: State HIV Prevalence from the National HIV/AIDS & Reproductive Health Survey (NARHS) in 2012, Nigeria

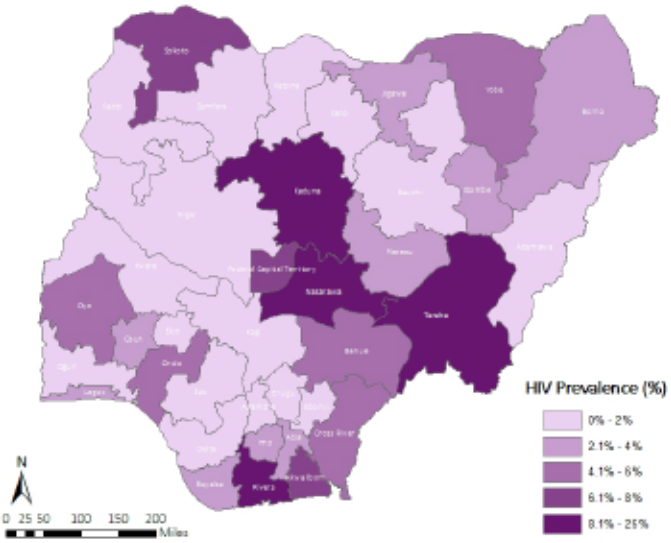


Figure 3-3: State HIV Prevalence from ANC Sentinel Surveillance in 2014, Nigeria

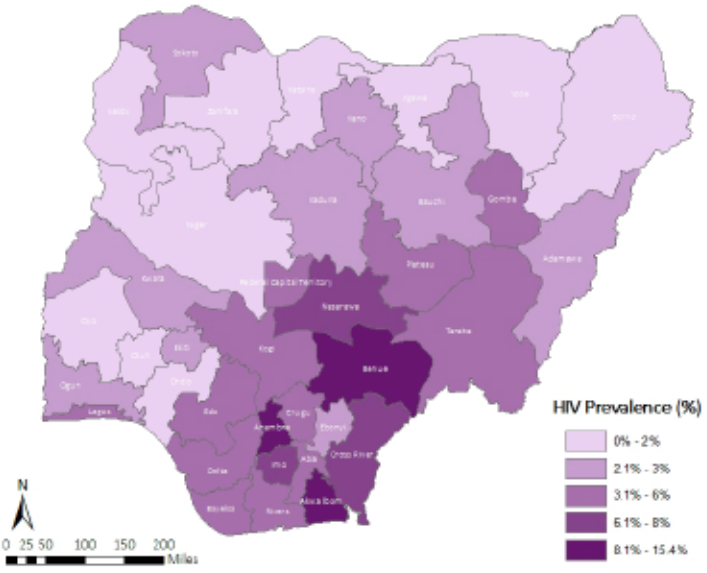
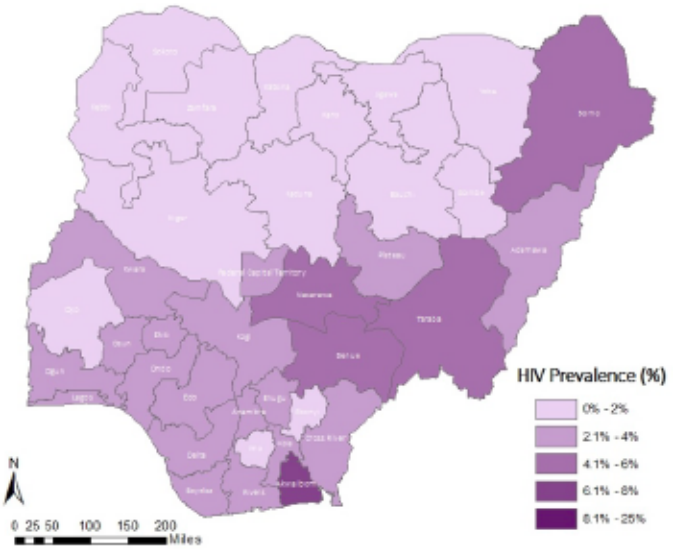


Figure 3-4: State HIV Prevalence from PEPFAR-Supported PMTCT Program Data (raw data, pre-modeling) in 2015, Nigeria



Little is known about the variability of HIV prevalence within states in Nigeria. Our analysis begins to address this gap in epidemiologic data by making use of a vast resource in PEPFAR PMTCT program data from 2.2 million pregnant women tested for HIV while attending antenatal care at 5,662 facilities across the country in fiscal year 2015. Understanding which local government areas (LGAs) have the highest HIV prevalence will aid in the prioritization of LGAs for scale-up of HIV interventions including, but not limited to, PMTCT programs.

Historically, the scientific consensus has been that program data are not "ready" to replace antenatal care sentinel surveillance and periodic population-representative surveys due to well-founded concerns about the quality and completeness of program

data when compared to survey or surveillance data.[13,16–25] Antenatal care sentinel surveillance uses unlinked anonymous testing to test 100% of women attending sentinel antenatal care sites, whereas PMTCT program participants may opt out of HIV testing, so the sample of women tested in PMTCT programs may not represent the complete population of women attending a given antenatal care site. This was a particularly well-founded concern when the bulk of the scientific literature on this topic was published, in the nineties and early 2000's. Today, PMTCT programs in most high burden countries are at national scale and there have been important operational and clinical simplification of PMTCT interventions,[26] particularly in the scale-up of provider initiated opt-out HIV testing at antenatal care.[27] In Nigeria, a mean of 93% (median: 100%) of antenatal care attendees were tested for HIV in PEPFAR-supported PMTCT sites in fiscal year 2015.[28] The World Health Organization released guidance recommending and describing the optimal use of routine PMTCT program data for descriptive epidemiologic purposes in 2015.[29] In 2017, roughly 75% of high burden countries incorporated routinely collected HIV testing data from PMTCT sites in the files used by UNAIDS to model HIV prevalence and incidence.

Within a single facility, routinely-collected program data may never be as complete and accurate as research data. But program data can offer a vast sample size and broad sampling frame that surveys cannot replicate. In fiscal year 2015, the PEPFAR program in Nigeria tested over 2.2 million pregnant women for HIV – this sample is over 62 times larger than the number of women tested in the latest population-representative survey

or antenatal care sentinel surveillance.[13,14,30] The enormity of the sample size may make up for the differential levels of accuracy within a given site.

Secondary analysis of routinely-collected programmatic data is less costly than conducting antenatal care sentinel surveillance or population-representative surveys to estimate HIV burden at the LGA level. It provides an exponential increase in the granularity of descriptive epidemiologic data, allowing for more precise targeting of interventions, without additional cost for collection of survey or surveillance data.

METHODS

Data sources & creation of analytic dataset

This analysis included two sources of data, described below: (1) published ANC sentinel surveillance data from 2014 in Nigeria, and (2) routinely collected HIV testing data from PMTCT sites supported by PEPFAR in Nigeria in fiscal year 2015.

ANC Sentinel Surveillance (ANC-SS) Data (2014)

Nigeria began conducting HIV sentinel surveillance through antenatal care in 1991.[31] The 2014 ANC Sentinel Surveillance Report represents the 9th round of sentinel surveillance. In 2014, a total of 36,431 pregnant women were tested for HIV at 160 ANC sites for sentinel surveillance, with a minimum of four sentinel surveillance sites (two urban and two rural) in each of 36 states plus the federal capital territory of Abuja. Table 3-2 summarizes the number of ANC sentinel surveillance sites and the number of

women tested through sentinel surveillance by state. ANC Sentinel Surveillance uses unlinked anonymous testing, meaning that 100% of patients attending ANC at sentinel sites are tested for HIV, but samples are not linked to individuals, and results are not returned to patients. Samples are taken at ANC sentinel sites, anonymized, and sent to state laboratories for HIV testing. The HIV rapid testing algorithm used in the 2014 ANC Sentinel Surveillance is the same testing algorithm used for the national PMTCT and HIV testing and counselling programs, with Determine (rapid diagnostic test for the detection of antibodies to HIV 1 and HIV 2) as the first line test. Stat-Pak (another HIV 1/2 antibody test) is used as a confirmatory test for positive samples, and in the case of discordant results, enzyme-linked immunosorbent assay (ELISA) is used as a tie-breaker.[31]

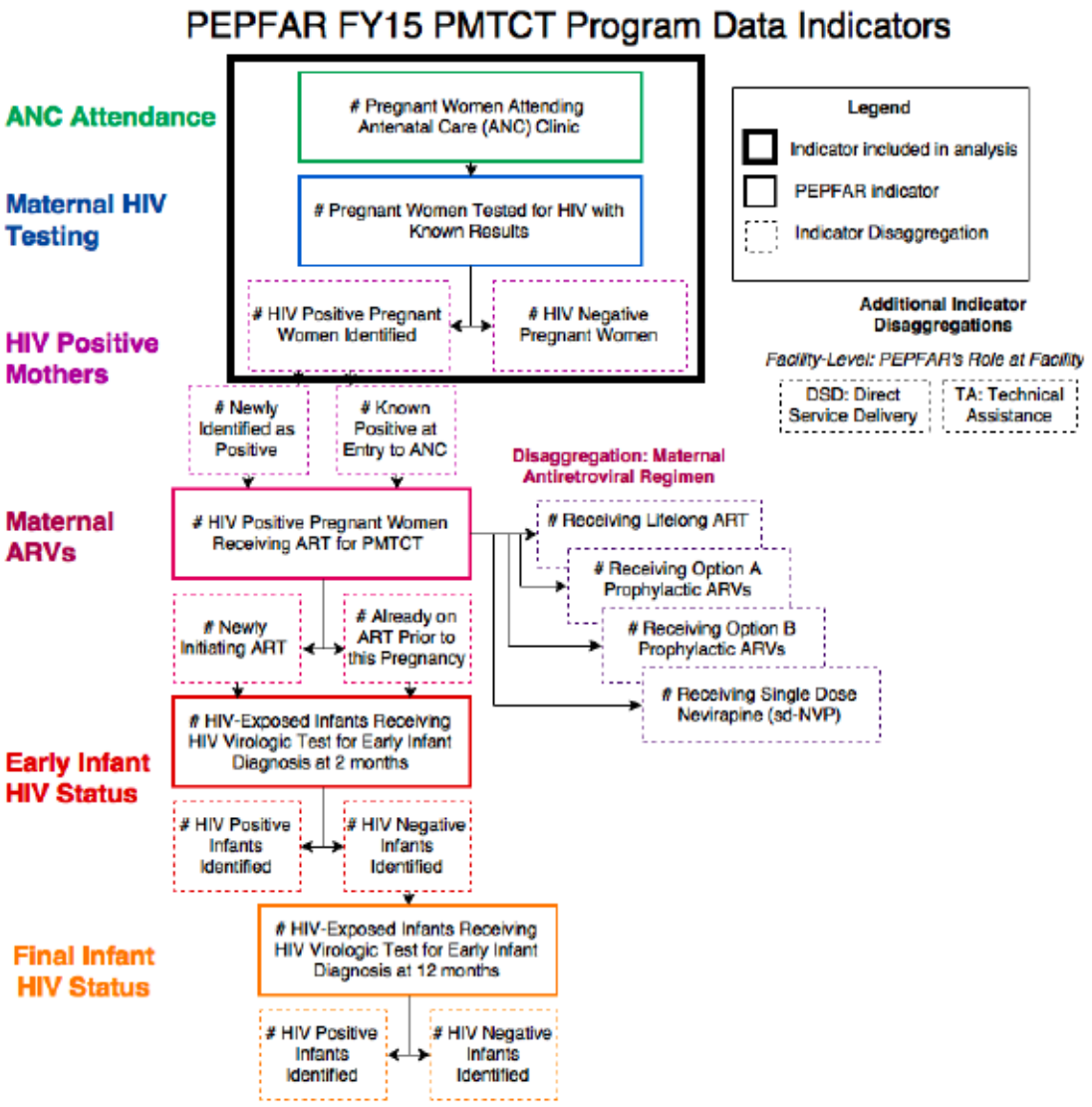
PEPFAR PMTCT program data (PMTCT data) (2015)

The PEPFAR PMTCT program data include facility-aggregated data from 2,237,055 pregnant women tested for HIV at 5,662 PEPFAR-supported PMTCT sites in Nigeria. These PMTCT sites are public, faith-based, or private health facilities offering antenatal care services which receive direct service delivery support from PEPFAR to offer PMTCT services. In fiscal year 2015, direct service delivery support was defined as: both (a) provision of key staff or commodities to the site, and (b) a minimum of 4 technical support site visits from a PEPFAR implementing partner per year.[32] All facilities included in our analytic dataset met these requirements. PMTCT program data at PEPFAR-supported PMTCT sites in Nigeria are collected at facilities in paper registries or via

electronic data systems. PEPFAR implementing partners enter site-level data into a global database each quarter. CDC and USAID teams in Nigeria review the data and work with partners to resolve any discrepancies before submission. Site level data are then reviewed at headquarters. PMTCT indicators collected through the PEPFAR monitoring evaluation and reporting system are summarized in Figure 3 5, and the dark box indicates which indicators were included in this analysis.

Until recently, PEPFAR's collection of data at the global level has been aggregated at the national (2004-2012), regional, or district levels (2013-2014). 2015 was the first year that facility-level data were reported to headquarters on a quarterly basis for every PEPFAR-supported country. These data are an immense resource with great potential for new analyses. Site-level PEPFAR PMTCT data are available for 12 months in fiscal year 2015 for 35 of the 37 states. Two states – Abia and Taraba – formally transitioned all PEPFAR-supported PMTCT sites to the Government of Nigeria in mid fiscal year 2015. Only 6 months of data are available for facilities in these two states.

Figure 3-5: PEPFAR PMTCT Indicators, fiscal year 2015



The HIV testing algorithm at PEPFAR-supported PMTCT sites is consistent with the national testing algorithm, and that used in ANC-SS as described above. All pregnant women attending ANC at PMTCT sites are counseled and offered an HIV test. On average, 93% (mean) of pregnant women accept the HIV test and receive their results.

Table 3-2: Number of Facilities and Number of Pregnant Women Tested for HIV through 2014 ANC Sentinel Surveillance and 2015 PEPFAR PMTCT Program Data in Nigeria

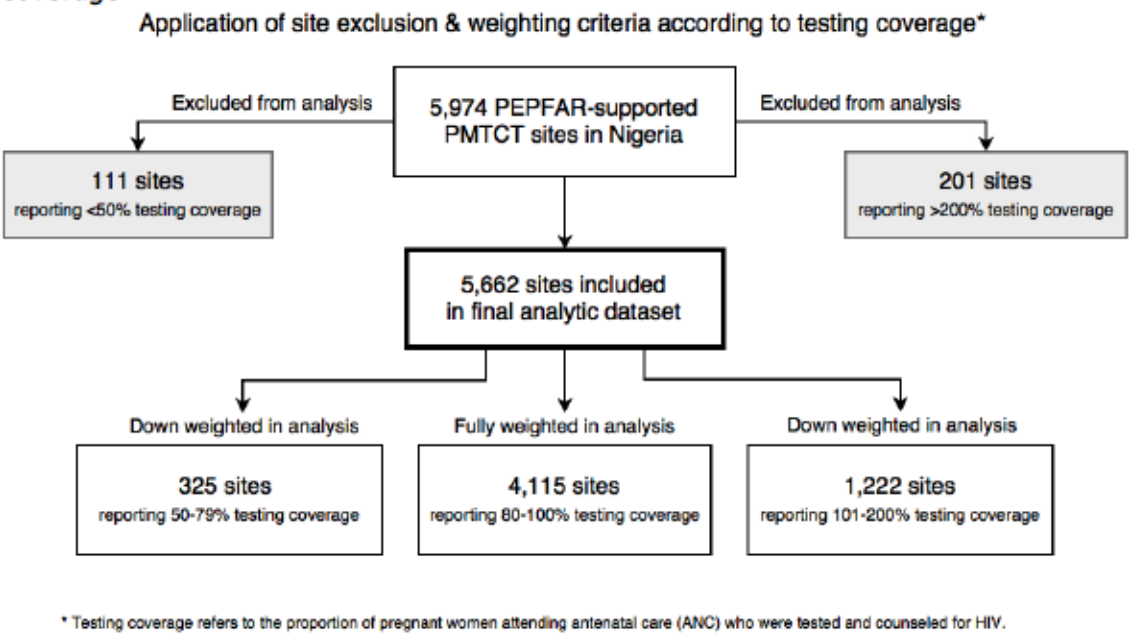
State	Number of PMTCT/ANC Sites in Datasets			Number of Pregnant Women Tested	
	ANC Sentinel Surveillance (ANC-SS) Data (2014)	PEPFAR PMTCT Program Data (2015)	ANC Sites with both ANC-SS Data & PEPFAR PMTCT Program Data	ANC Sentinel Surveillance Data (2014)	PEPFAR PMTCT Program Data (2015)
Abia	4	340	1	899	11,669
Adamawa	4	16	4	896	15,873
Akwa Ibom	4	340	2	923	37,997
Anambra	5	304	1	1,181	36,632
Bauchi	4	40	3	898	34,057
Bayelsa	4	86	2	900	5,765
Benue	5	445	4	1,172	276,377
Borno	4	4	1	899	3,973
Cross River	4	432	3	900	25,188
Delta	4	48	2	898	45,426
Ebonyi	4	163	3	900	75,121
Edo	4	36	3	812	17,295
Ekiti	4	30	1	900	11,270
Enugu	5	266	4	954	71,717
FCT	5	214	4	1,199	100,090
Gombe	4	188	3	900	107,230
Imo	4	285	1	898	94,290
Jigawa	4	32	3	900	43,921
Kaduna	5	422	4	1,190	350,494
Kano	5	270	5	1,200	185,368
Katsina	4	15	4	900	32,988
Kebbi	4	27	4	900	30,761
Kogi	4	198	2	900	53,766
Kwara	4	27	2	871	28,251
Lagos	7	267	2	1,650	55,120
Nasarawa	4	180	4	895	74,786
Niger	4	112	2	900	66,248
Ogun	4	44	3	900	27,122
Ondo	4	52	4	900	37,143
Osun	4	25	0	900	11,781
Oyo	5	170	2	1,200	91,230
Plateau	4	230	3	890	78,838
Rivers	5	264	3	1,323	25,929
Sokoto	4	10	3	900	20,562
Taraba	4	55	1	896	8,930
Yobe	5	5	1	1,200	12,003
Zamfara	4	20	1	887	31,844
State Average (Mean)	**4**	**153**	**3**	**985**	**60,461**
TOTAL	**160**	**5,662**	**95**	**36,431**	**2,237,055**

Application of site exclusion criteria & weighting criteria for PMTCT Program Data

A total of 5,974 sites received direct service delivery support from PEPFAR in fiscal year 2015, had complete data, and were eligible for inclusion in the analysis. Sites reporting that greater than 200% or less than 50% of pregnant women attending antenatal care were tested for HIV were excluded from the analysis because the positivity rate as measured at these facilities may not be representative of true HIV positivity among women attending these sites due to serious data quality issues (under- or over-reporting the number of women tested for HIV), or operational concerns such as long term stock-outs of HIV test kits, or HIV testing campaigns that took place outside of the health facility setting and could represent a biased sample. The 5,662 remaining sites were included in the analytic dataset. Of these, sites reporting testing between 80-100% of pregnant women at antenatal care for HIV were fully weighted, while sites reporting 50-79% or 101-200% of pregnant women attending antenatal care were tested for HIV were down-weighted on a categorical scale. Figure 3-6 describes the application of site exclusion and weighting criteria for the analytic dataset. Sites reporting 50-79% or 101 - 200% of antenatal care attendee testing coverage were divided into four quartiles and weighted: quartile 1 (least extreme) was assigned a weight of 80%; quartile 2 a weight of 60%; quartile 3 a weight of 40%; and quartile 4 (most extreme) a weight of 20%. Quartiles were used for the weighting procedure given that proportion of pregnant women tested for HIV is not normally distributed, and use of a non-parametric scale is therefore more appropriate than a parametric (continuous) scale. However, we also

explored the use of a continuous weighting scale rather than the use of quartiles, and this did not significantly change the results (data not shown). After application of site exclusion and weighting criteria, data from a total of 5,662 PEPFAR-supported PMTCT sites were included in the final analytic dataset.

Figure 3-6: Application of site exclusion and weighting criteria according to testing coverage



* Testing coverage refers to the proportion of pregnant women attending antenatal care (ANC) who were tested and counseled for HIV.

Analytic Methods

Objective 1: *Compare facility- and state-level HIV prevalence estimates based on ANC-SS to estimates based on PMTCT program data*

HIV prevalence estimates from 95 facilities with data available from both data sources were compared to evaluate the difference between facility-level HIV prevalence measured through routine PMTCT program data at PEPFAR-supported sites in fiscal year

2015 (PMTCT data) and through ANC sentinel surveillance (ANC-SS) in Nigeria in 2014. Nigeria's 2014 ANC-SS report lists facility-level HIV prevalence estimates by site and state, but facility names are abbreviated. However, Nigeria's 2010 ANC-SS report includes a comprehensive list of sentinel surveillance sites by state complete with facility names. Given that ANC-SS sites in Nigeria have been consistent over time, these two documents were used together to generate a list of facilities and 2014 results. Facility names from the published ANC-SS reports (n = 160 facilities) were matched with facilities reporting PMTCT testing results through PEPFAR's monitoring evaluation and reporting system from fiscal year 2015 (n=5,662 facilities). A total of 95 of the 160 ANC-SS sites were successfully matched with PEPFAR PMTCT sites (59% of eligible sites), and data from these 95 sites formed the basis of the analytic dataset for Objective 1.

Exploratory analyses were used to compare the distribution of HIV prevalence at the facility and state levels for the 95 sites that were matched versus the 65 ANC-SS sites that did not provide PMTCT services with PEPFAR support, and these relationships were visualized using box plots. The absolute difference between site level prevalence estimates was calculated by subtracting the PEPFAR PMTCT prevalence estimates from the ANC-SS prevalence estimates. Exploratory data analyses were used to calculate summary statistics and visualize the absolute difference data by site using a column graph. Two-way scatterplots were used to visualize the relationship between HIV prevalence estimated using ANC-SS versus PEPFAR PMTCT program data, and Bland-

Altman plots were used to compare the HIV prevalence estimates from ANC-SS to PEPFAR PMTCT program estimates.

A series of multiple linear regression models were used to assess the association between the two sets of HIV prevalence estimates, and explore what other factors may explain the difference between these two estimates. Specifically, regression analyses were used to assess each the following factors as secondary associations of interest: urban versus rural location of the facility, the geographic location of the facility (North versus South), the PEPFAR implementing partner supporting the facility, the United States Government Agency supporting the PMTCT program, the overall patient volume at the facility, the volume of HIV positive patients at the facility, and State HIV prevalence (based on PEPFAR PMTCT program data). The number and proportion of facilities with HIV prevalence estimates from PEPFAR PMTCT program data that fell outside of the 95% confidence intervals from the published ANC-SS HIV prevalence estimates was assessed and recorded. Finally, state-level HIV prevalence estimates from ANC-SS data were compared to state-level estimates based on PEPFAR PMTCT program data. Summary statistics were generated to characterize the differences, and two-way scatterplots and Bland-Altman plots were used to visualize the differences between state-level HIV prevalence estimates from the two data sources.

Objective 2: *Estimate LGA-level HIV prevalence among pregnant women attending ANC at PEPFAR-supported PMTCT sites in Nigeria in 2015.*

Using the analytic dataset described above with routine PMTCT program data from PEPFAR-supported facilities (n=5,662 sites, 2,237,055 pregnant women tested for HIV) in fiscal year 2015, HIV prevalence estimates were generated for 616 LGAs in Nigeria, and the within-state distribution of HIV was described. See Table 3-4 for a summary of the PMTCT program data included in the analytic dataset by state.

Empirical Bayes Estimation techniques and a multilevel logistic regression model with a binomial distribution and random intercepts at the LGA and site levels were used to extrapolate site prevalence estimates and estimate LGA HIV prevalence estimates. Random intercepts were assumed to be normally distributed with a mean of 0 and a variance of σ^2. Empirical Bayes Estimation techniques give more weight to the data from higher volume facilities and "shrink" site prevalence at the lower volume facilities towards the LGA and state mean values, thus reducing the impact of outliers or extreme data on our estimates.

The full statistical model described above was used for 24 of the 37 states. For the remaining 13 states, the model was over-parameterized, so the model was run without the site-level random effect for those states. HIV prevalence estimates and 95% confidence intervals were calculated around the mean LGA estimates of HIV prevalence

among pregnant women attending antenatal care at PEPFAR-supported sites for each LGA. The Empirical Bayes-modeled estimates were then used to generate state-level HIV prevalence estimates based on the frequency-weighted mean LGA HIV prevalence. Frequency weights were based on the number of pregnant women tested per LGA. ARC GIS software, version 10.4[33] was used to create choropleth maps with states and LGAs shaded according to burden of HIV based on estimated HIV prevalence among pregnant women attending antenatal care at PEPFAR supported sites.

Descriptive statistics and scatterplots were used to characterize the location, spread, and shape of the distribution of LGA-level HIV prevalence estimates and confidence intervals within each state. The number of states containing LGAs with 95% confidence intervals for estimated HIV prevalence that do not overlap was also quantified, indicating a statistically significant difference between the highest and lowest prevalence LGAs within these states. All analyses were completed using Stata MP 2 cores, version 14.2.[34]

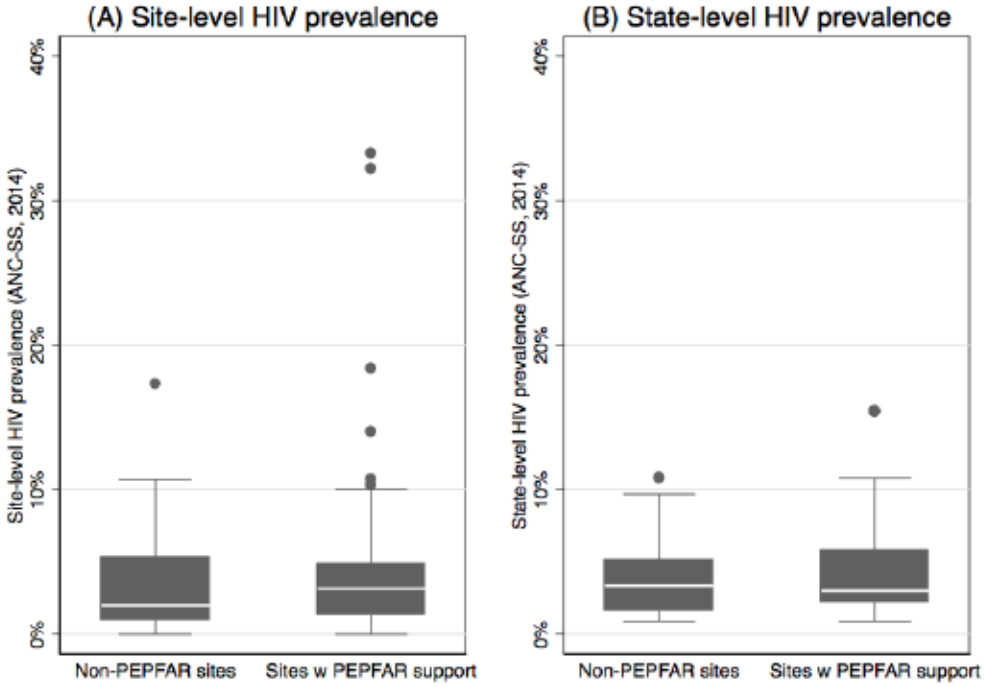
RESULTS

Objective 1: *Compare facility- and state-level HIV prevalence estimates based on ANC-SS to estimates based on PMTCT program data*

No significant systematic differences were found between the site-level or state-level HIV prevalence at the 95 ANC-SS sites with PEPFAR-supported PMTCT programs that comprised the analytic dataset compared to the 65 ANC-SS sites without PEPFAR-

supported PMTCT programs which were excluded from this analysis (see Figure 3-7). The sample of 95 sites included in the analytic dataset is free of known biases and is assumed to be generally representative of all 160 ANC-SS sites.

Figure 3-7: HIV prevalence estimates from ANC sentinel surveillance (ANC-SS) data at (A) site-level and (B) state-level, comparing the 65 ANC-SS sites without PEPFAR support (sites excluded from the analytic dataset) to the 95 ANC-SS sites with PEPFAR support for PMTCT services in Nigeria (sites included in the analytic dataset)



Subtracting the HIV prevalence estimate from PEPFAR PMTCT program data from the estimate based on ANC Sentinel Surveillance data yielded a small mean difference in HIV prevalence at the facility level of 0.11%, 95% CI: [-0.66%, 0.87%], but a large standard deviation and variance: 3.76% and 14.14%. The median difference was small -0.06%, inner quartile range (IQR): [-1.16, 1.35] but with a wide range [-13.19, 23.15]. Figure 3-8 displays the difference in HIV prevalence estimates between PEPFAR PMTCT program

data and ANC-SS data for each of the 95 sites. While there were large differences at some sites and moderate differences in HIV prevalence at many sites, there was no clear pattern in the distribution of differences of HIV prevalence estimates between the two data sources. Exactly half of the sites had higher prevalence in PEPFAR's program data than was reported through sentinel surveillance, while half had lower prevalence. The mean absolute value of the difference in prevalence estimates between the two data sources was 2.16%, 95% CI: [1.53%, 2.79%], standard deviation: 3.07%, and variance: 9.44%. The median absolute value of the difference in prevalence estimates was 1.22%, IQR: [0.58%, 2.53%], and range: [0%, 23.15%]. Approximately 36% of sites (34 of 95 sites) had PMTCT prevalence estimates beyond the 95% confidence interval published in ANC-SS, meaning they were statistically significantly different. Of these, 12 sites had PMTCT prevalence significantly above ANC-SS, and 22 sites had PMTCT prevalence significantly below ANC-SS.

Figure 3-8: Difference between HIV prevalence estimates at the facility level in Nigeria (ANC Sentinel Surveillance (2014) estimates - PEPFAR PMTCT Program (2015) estimates)

The results of this analysis indicate that there are substantial differences between site-level HIV prevalence estimates generated for PEPFAR PMTCT program data compared to prevalence estimates from ANC-SS data. Figure 3-9 includes a pair of two-way scatterplots that visually display this relationship, with Graph A showing data for all 95 sites, and Graph B excluding sites with extreme values (estimated HIV prevalence >15%). Ideally, we would expect to see a 1:1 relationship between prevalence estimates from these two sources. These graphs demonstrate a weak linear relationship between HIV prevalence estimates from PMTCT program data and ANC-SS, but there is substantial scatter, indicating wide variation between the two prevalence estimates at many sites. Figure 3-10 is a Bland-Altman plot displaying the relationship between HIV prevalence estimates from PMTCT program data and ANC-SS data. While the average (mean) difference is close to zero, this is due to the presence of positive and negative absolute differences. The interval containing 95% of the data (+/- 2 standard deviations) is wide (-7.413, 7.629), and the variance is much larger than the mean value. This suggests that there are important positive and negative difference between HIV prevalence estimates generated through ANC-SS compared to PMTCT program data within a given health facility. Within a given site, these differences may be due to systematic or random error, but there is not a clear pattern in these differences across facilities.

Figure 3-9: Two-way Scatterplots: Site-Level HIV Prevalence from PEPFAR PMTCT Program (2015) versus ANC Sentinel Surveillance (2014) in Nigeria, with complete data (Graph A) and excluding extreme values (HIV prevalence >15%) (Graph B)

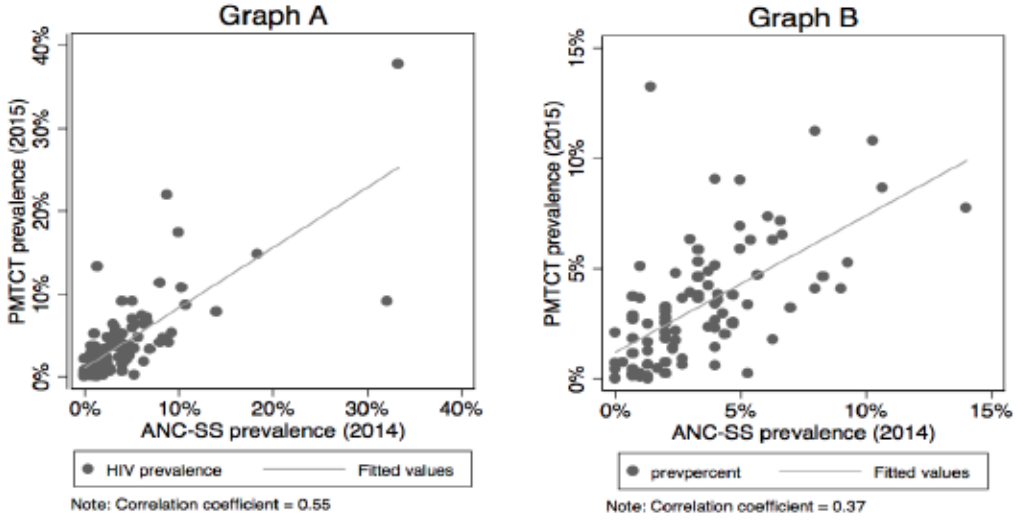
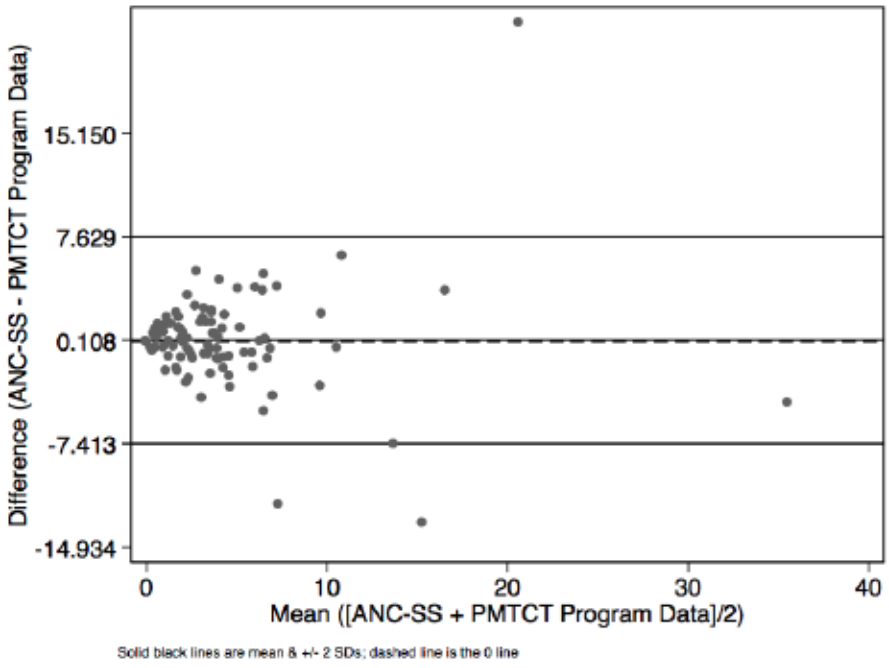


Figure 3-10: Bland-Altman Plot Comparing Site-Level HIV Prevalence Estimates (%) from ANC Sentinel Surveillance (ANC-SS) (2014) to PEPFAR PMTCT Program Data (2015) in Nigeria

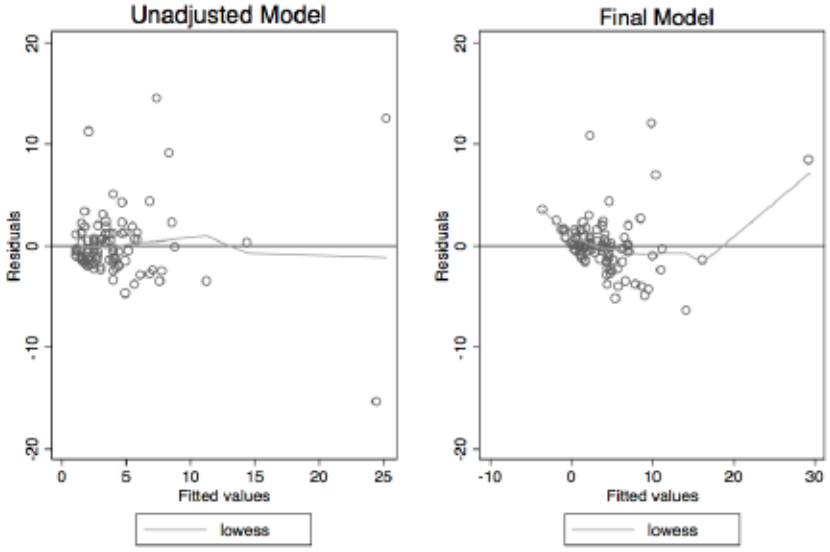


A series of linear regression models were used to analyze the association between site-level PMTCT program prevalence and site-level ANC sentinel surveillance prevalence, and to assess the extent to which other covariates of interest may explain the differences between PMTCT program prevalence and ANC-SS prevalence. The results of select linear regression models are summarized in Table 3-3. Total patient volume at ANC and HIV positive patient volume were statistically significantly associated with PMTCT program prevalence, and there was statistical interaction between ANC-SS prevalence and HIV positive patient volume. There was no statistically significant association between PMTCT program prevalence and urban/rural location, geographic location in the North versus South of the country, PEPFAR implementing partner, US Government agency supporting the site, or state HIV prevalence based on PMTCT program data, so these were excluded from our final model. A parsimonious model with the lowest Akaike's Information Criteria (AIC) value (474.359) was selected as the final prediction model. Controlling for total patient volume, the volume of HIV positive patients, and the statistical interaction between ANC-SS and HIV positive patient volume, we found that on average for every 1% increase in PMTCT program prevalence, we would expect a 0.98% increase in ANC-SS prevalence. The Pearson's Correlation Coefficient (R^2) from the unadjusted model indicates that ANC-SS alone explains approximately 54.7% of variation in PMTCT program prevalence. The combination of covariates in the final model explains 70.5% of the variation in PMTCT prevalence. Figure 3-11 is a pair of residuals versus fitted plots displaying the improvement in model fit comparing the unadjusted linear regression to the final model.

Table 3-3: Results of select linear regression models

	Outcome	Covariates	Coefficients	95% CI	p-value	R^2	AIC
Model A: Unadjusted SLR	PMTCT program prevalence	ANC-SS	0.73	0.59, 0.86	<0.01	0.55	509.21
Model B: Patient volume	PMTCT program prevalence	ANC-SS Total # patients	0.73 0.00	0.60, 0.86 -0.01, 0.01	<0.01 <0.01	0.61	497.40
Model C: HIV+ patients	PMTCT program prevalence	ANC-SS # HIV+ patients	0.90 -0.02	0.73, 1.08 -0.25, -0.01	<0.01 0.003	0.59	502.21
Model D: Final model w interaction term	PMTCT program prevalence	ANC-SS Total # patients # HIV+ patients ANC-SS * HIV+ patients	0.98 -0.01 0.21 0.00	0.80, 1.16 -0.00, -0.00 0.01, 0.04 -0.60, 1.74	<0.01 <0.01 0.01 <0.01	0.71	474.36

*Figure 3-11: Residuals vs Fitted Plots for unadjusted model (simple linear regression of ANC-SS prevalence on PMTCT program prevalence), and final model (multiple linear regression of ANC-SS prevalence, total patient volume, HIV+ patient volume, statistical interaction term for ANC-SS prevalence * HIV+ patient volume on PMTCT program prevalence)*



State-Level Analysis

Finally, differences in state-level HIV prevalence between ANC-SS data and PEPFAR PMTCT program data were assessed. The absolute difference between state-level HIV prevalence estimates was calculated, subtracting PEPFAR program data prevalence from ANC-SS prevalence. ANC-SS state HIV prevalence was on average (mean) 1.8% higher than PMTCT program state prevalence, 95% CI: [1.3%, 2.3%], with standard deviation of 2.4% and variance of 0.1%. Compared to ANC-SS-based state HIV prevalence estimates, PMTCT data-based state prevalence was lower in 29 states, exceeded ANC-SS in 5 states, and was equal in two states. The median difference in prevalence at the state level was 1.3%, IQR: [0.5%, 2.3%], range: [-1.4%, 11%]. Figure 3-12 displays the difference in HIV prevalence by state.

Figure 3-12: Difference in state HIV prevalence estimates in Nigeria, subtracting PMTCT program data-based estimates (2015) from ANC sentinel surveillance-based estimates (2014)

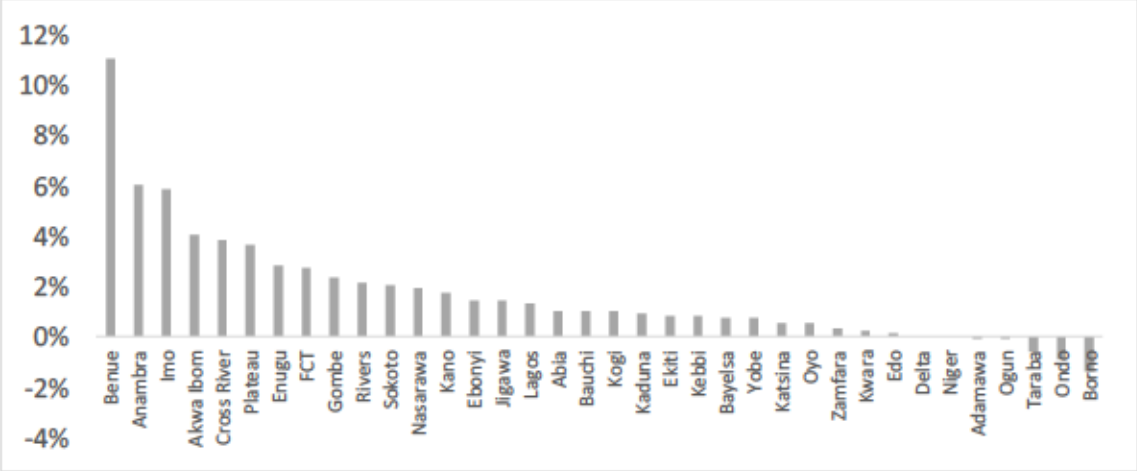


Figure 3-13 is a two-way scatterplot comparing state-level HIV prevalence from PMTCT program data to state-level HIV prevalence from ANC-SS data, with a regression line.

The graph suggests that the relationship between the two sets of state prevalence estimates is roughly linear, with a slope of less than 1, indicating that ANC-SS state prevalence estimates tend to be higher than PMTCT program state prevalence estimates. A single linear regression of state ANC-SS prevalence on state PMTCT program prevalence indicates that on average for every 1% increase in ANC sentinel surveillance state HIV prevalence, we would expect a 0.31% increase in PEPFAR PMTCT program state prevalence, 95% CI: [0.23% to 0.38%]. A Bland-Altman Plot (Figure 3-14), documents the systematic overestimation in ANC-SS prevalence estimates at the state level, compared to estimates based on PMTCT program data.

Figure 3-13: Two-way Scatterplot: State-Level HIV Prevalence from PEPFAR PMTCT Program (2015) versus ANC Sentinel Surveillance (2014) in Nigeria

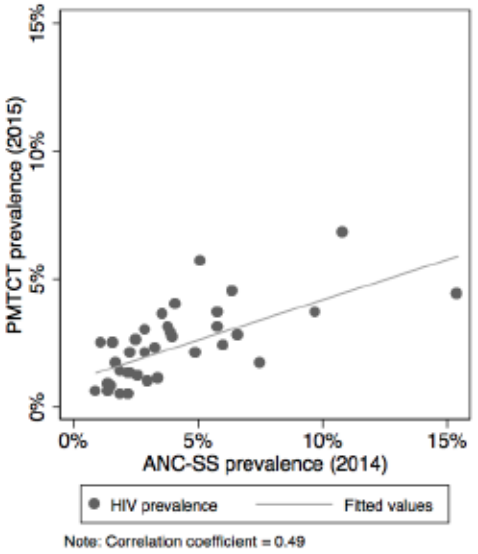
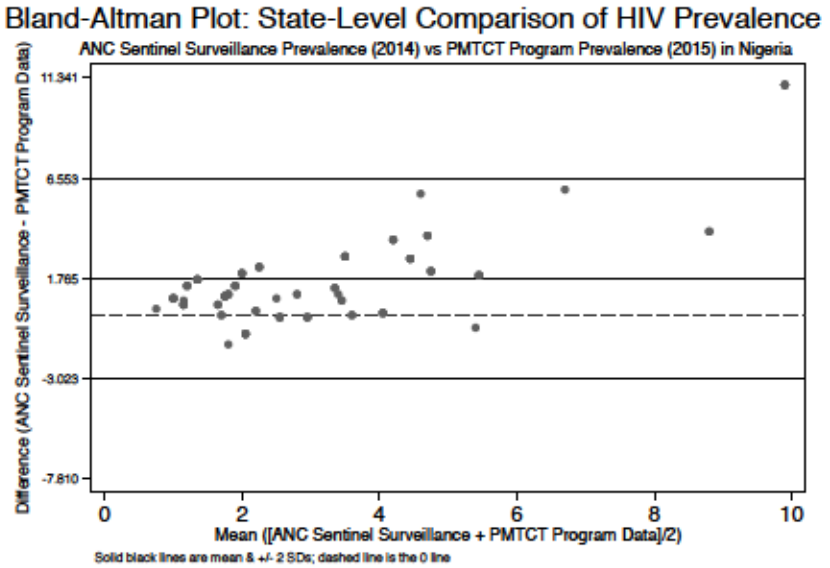


Figure 3-14: Bland-Altman plot: State-level comparison of HIV prevalence (ANC sentinel surveillance-based prevalence (2014) versus PMTCT program data-based prevalence (2015) in Nigeria)



Objective 2: *Estimate LGA-level HIV prevalence among pregnant women attending ANC at PEPFAR-supported PMTCT sites in Nigeria in 2015.*

Table 3-4 summarizes the analytic dataset used for this analysis.

Table 3-4: Number of LGAs and health facilities supported by PEPFAR to provide PMTCT services, number of pregnant women tested with PEPFAR support, and percent of pregnant women testing positive for HIV (raw un-modeled PMTCT data), by state in Nigeria, fiscal year 2015

State	PEPFAR-supported LGAs (#)	PEPFAR-supported health facilities offering PMTCT services (#)	Pregnant women tested for HIV (#)	Pregnant women identified as HIV positive (%)
Abia	17	340	11,669	2.9%
Adamawa	13	16	15,873	2.6%
Akwa Ibom	31	340	37,997	6.8%
Anambra	21	304	36,632	3.7%
Bauchi	15	40	34,057	1.3%
Bayelsa	8	86	5,765	3.1%
Benue	23	445	276,377	4.4%
Borno	4	4	3,973	2.5%
Cross River	18	432	25,188	2.8%
Delta	24	48	45,426	3.6%
Ebonyi	13	163	75,121	1.2%
Edo	15	36	17,295	4.0%
Ekiti	16	30	11,270	2.1%
Enugu	17	266	71,717	2.1%
FCT	6	214	100,090	3.1%
Gombe	11	188	107,230	1.1%
Imo	27	285	94,290	1.7%
Jigawa	14	32	43,921	0.5%
Kaduna	23	422	350,494	1.3%
Kano	38	270	185,368	0.5%
Katsina	11	15	32,988	0.9%
Kebbi	12	27	30,761	0.6%
Kogi	20	198	53,766	2.3%
Kwara	8	27	28,251	2.1%
Lagos	20	267	55,120	2.7%
Nasarawa	13	180	74,786	4.5%
Niger	24	112	66,248	1.7%
Ogun	16	44	27,122	3.0%
Ondo	18	52	37,143	2.5%
Osun	12	25	11,781	2.1%
Oyo	33	170	91,230	1.4%
Plateau	17	230	78,838	2.4%
Rivers	23	264	25,929	3.7%
Sokoto	7	10	20,562	1.0%
Taraba	15	55	8,930	5.7%
Yobe	5	5	12,003	0.8%
Zamfara	8	20	31,844	0.6%
TOTAL	**616**	**5,662**	**2,237,055**	**2.3%**

LGA-level HIV prevalence estimates with 95% confidence intervals were generated for each of 616 LGAs with PEPFAR-supported PMTCT sites. These Empirical Bayes-modeled estimates range from a low of 0.0% prevalence to a high of 11.2% prevalence.

The mean difference between the highest and lowest prevalence LGAs within states was 3.6%. Our results indicate that 62% of states (23/37) have statistically significant differences in LGA prevalence values meaning the 95% CIs for highest and lowest prevalence LGAs do not overlap. These results are summarized in Table 3-5. The 14 states without a statistically significant difference in within-state LGA HIV prevalence estimates may be due to either true lack of variability in HIV prevalence within the state, low programmatic coverage yielding sparsely available PMTCT program data for few LGAs, or wide confidence intervals due to sparse or varied data within a state.

Table 3-5: Variation in within-state LGA HIV prevalence in Nigeria

States with statistically significant difference between estimated HIV prevalence in highest & lowest prevalence LGAs within state	Adamawa, Akwa Ibom, Anambra, Benue, Borno, Cross River, Ebonyi, Edo, FCT (Abuja), Gombe, Jigawa, Kaduna, Kano, Katsina, Kogi, Kwara, Nasarawa, Niger, Ondo, Oyo, Plateau, Sokoto, Yobe
States with no statistically significant difference between estimated HIV prevalence highest & lowest prevalence LGAs within state	Abia, Bauchi, Bayelsa, Delta, Ekiti, Enugu, Imo, Kebbi, Lagos, Ogun, Osun, Rivers, Taraba, Zamfara

Figure 3-15 (raw data) and Figure 3-16(Empirical Bayes modeled estimates) display our results visually through scatterplots, with the distribution of state HIV prevalence on the

y axis and the distribution of LGA HIV prevalence on the x axis. Each horizontal row of diamonds represents a state, and each diamond represents the HIV prevalence of an LGA. Compared to the raw PMTCT prevalence estimates (Figure 3-15), the Empirical Bayes-modeled estimates (Figure 3-16) are more conservative, given that the statistical models account for clustering at the state, LGA, and facility levels, thus reducing the effect of extreme values on modeled prevalence estimates. For sites and LGAs with little available data, Empirical Bayes modeled estimates are "shrunk" towards mean values, thus borrowing strength from larger sites or LGAs with more data available. Visually, this is evident in that the within-state distribution of LGA HIV prevalence is wider in the raw, un-modeled data (Figure 3-15), and narrower in the modeled estimates (Figure 3-16).

Prevalence estimates are most precise (narrow 95% CIs) for LGAs in which PEPFAR supported HIV testing for a large number of pregnant women across a number of health facilities. The results are least robust and least meaningful in states where PEPFAR's support for PMTCT is limited, and the numbers of women tested and health facilities supported are lower. In general, states with higher HIV prevalence tended to have a wider variation in within-state LGA HIV prevalence.

Figure 3-15 and Figure 3-16 demonstrate the range of LGA-level HIV prevalence within these states. Akwa Ibom and Benue states – the two states with the highest state HIV prevalence using the Empirical Bayes-modeled estimates – have been highlighted in

these figures to demonstrate that even in the highest burden states, there are geographic areas with low HIV prevalence. Both states demonstrate a wide range of LGA HIV prevalence estimates using the raw PMTCT data, and Benue is the state with the widest range of Empirical Bayes modeled LGA HIV prevalence estimates while Akwa Ibom displays greater shrinkage towards mean prevalence estimates. Similarly, the state and LGA HIV prevalence choropleth maps show the range of HIV prevalence at the state level (Figure 3-17), and within states at the LGA level (Figure 3-18). We have again highlighted the examples of Akwa Ibom and Benue states on these maps to show the variation in within-state HIV prevalence in two high prevalence states.

Figure 3-15: Raw (un-modeled site-level PMTCT testing data): Distribution of state vs LGA HIV prevalence among women tested at ANC in PEPFAR-supported PMTCT sites in Nigeria in fiscal year 2015

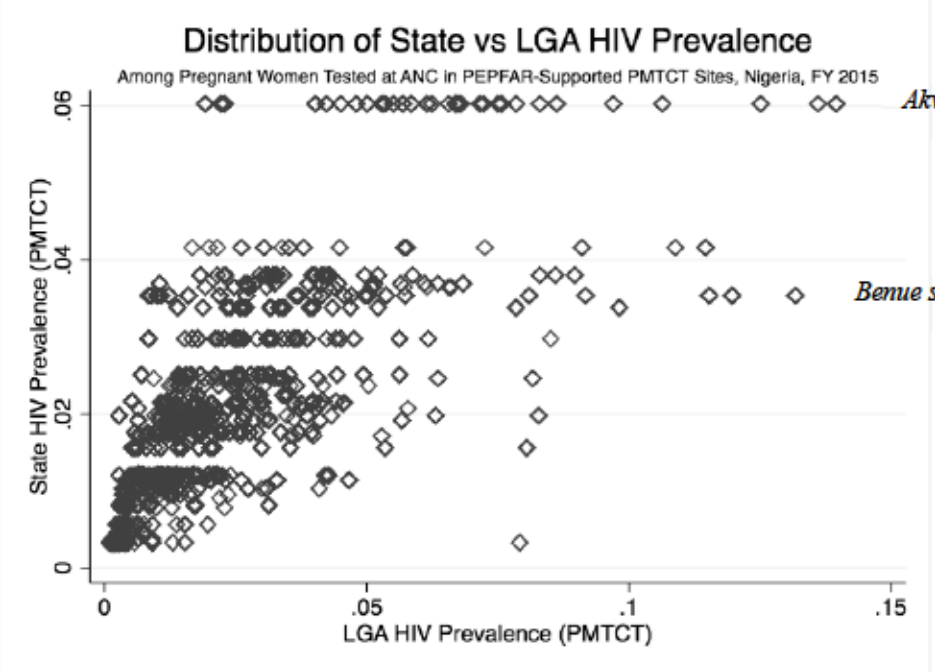


Figure 3-16: Empirical Bayes-modeled site-level PMTCT testing data: Distribution of state vs LGA HIV prevalence among women tested at ANC in PEPFAR-supported PMTCT sites in Nigeria in fiscal year 2015

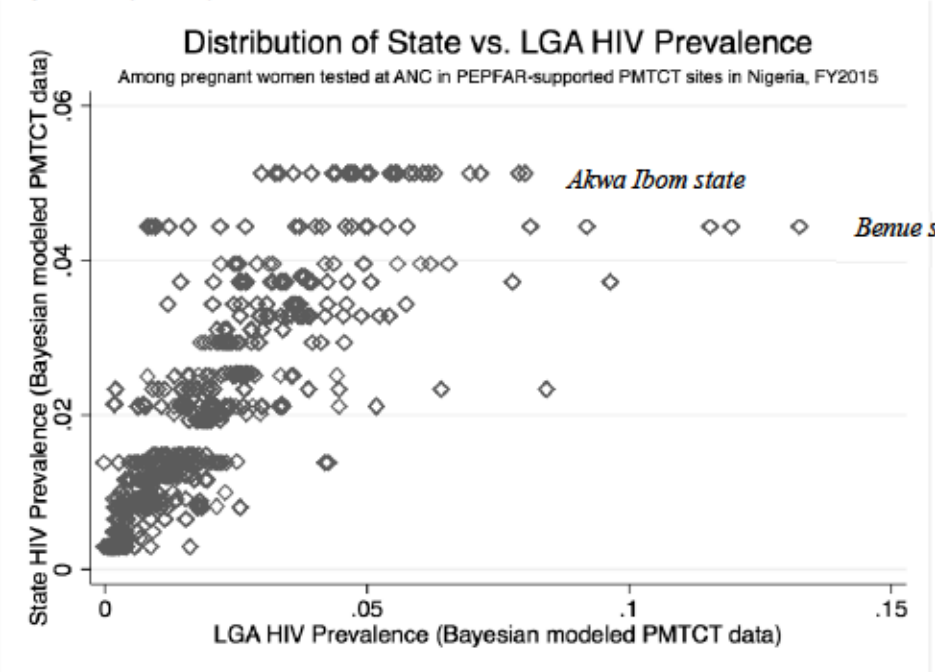


Figure 3-17: HIV prevalence by state, based on Empirical Bayes modeled PMTCT program data from PEPFAR-supported facilities, FY 2015

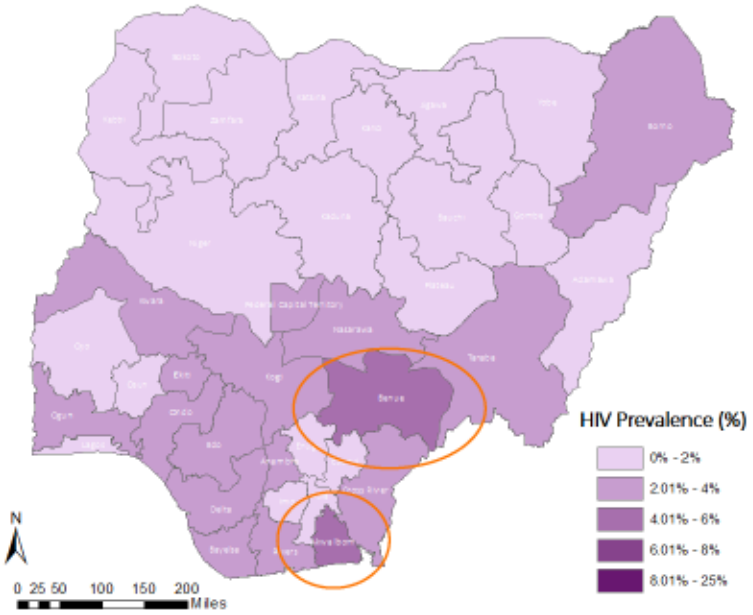
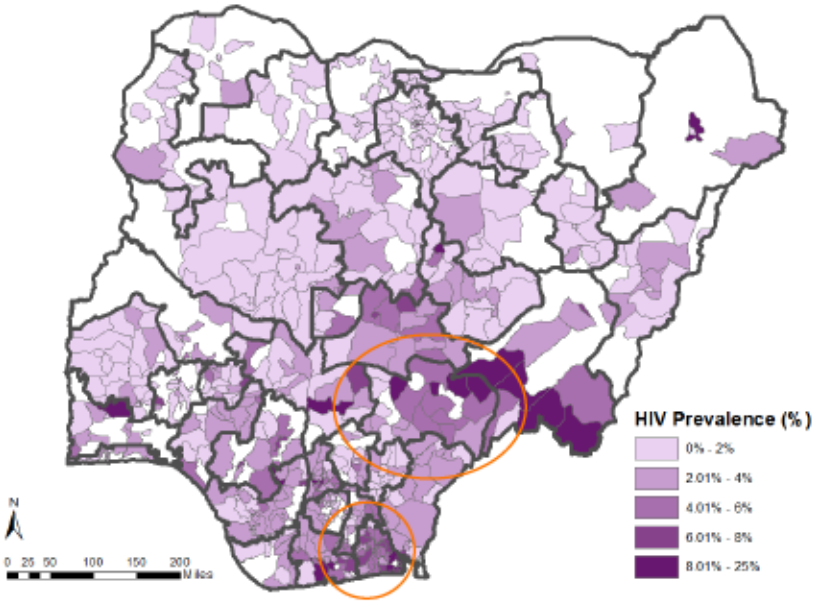


Figure 3-18: Nigeria: HIV prevalence by LGA, based on Empirical Bayes modeled PMTCT program data from PEPFAR-supported facilities, FY 2015



DISCUSSION

Objective 1: *Compare facility- and state-level HIV prevalence estimates based on ANC-SS to estimates based on PMTCT program data*

The results of this analysis indicate that there are significant differences between published ANC sentinel surveillance HIV prevalence estimates and HIV prevalence estimates based on routinely collected PMTCT program data in Nigeria. While mean difference between the two sets of prevalence estimates at the site level is close to zero, this is due to the presence of positive and negative differences. The variance (14.14%) and standard deviation (3.76%) are large and such differences are clinically meaningful, as is the average absolute value of the site-level difference in estimates (2.16%). HIV prevalence estimates at about one third of sites are statistically significantly different between the two sources of data, yet the wide variation observed at the site level does not follow an apparent pattern.

The state level analysis provided clear evidence of bias, with ANC-SS prevalence estimates on average 1.8% higher than PMTCT program-based estimates. A difference of this magnitude is critical in the context of Nigeria's low HIV prevalence epidemic (3.1% national HIV prevalence).[1] The fact that at the site level, a wide range of both positive and negative differences between the two sources of data exist in a seemingly random pattern but when aggregated at the state level, a clear bias emerges suggests

that the population of pregnant women attending ANC-SS sites may not be representative of the population of pregnant women attending ANC in the state. ANC-SS-based HIV prevalence estimates appear to be systematically over-estimating HIV prevalence in Nigeria. We recommend that future HIV prevalence estimates in Nigeria be generated using all available HIV testing data from all ANC sites, and not only testing data from the ANC-SS sites which are likely a biased sample of pregnant women attending ANC.[23] This analysis should be repeated for other countries to determine whether use of census PMTCT program data (from all PMTCT sites in a country) is necessary or whether use of routine PMTCT program data from historic ANC-SS sites alone sufficiently characterizes HIV epidemic. Caution should be exercised when using published ANC sentinel surveillance-based estimates for HIV program planning in Nigeria given these biases.

There are several important limitations to this analysis. First, 60% of ANC-SS sites were supported by PEPFAR in 2015, while 40% were not. The analytic dataset was limited to the 60% of sites that overlapped between the two data sources. While exploratory analyses were conducted to rule out obvious biases based on site-level or state-level HIV prevalence, we cannot guarantee that the results of the analysis on the 60% of sites that have both PEPFAR PMTCT program data and ANC-SS data represent all ANC-SS sites. Second, some of the analyses may have been limited by measurement error. For example, the assessment of the impact of urban versus rural location was based on the urban-rural classification of sites in the ANC-SS reports. Due to rapid urbanization in

some parts of the country, the ANC-SS sites designated as rural in 1993 may not be truly representative of rural populations today. Lastly, PEPFAR PMTCT program data were collected over a twelve-month period in fiscal year 2015, while ANC-SS data were collected over a three-month period in 2014. While the data from these sources represent the same general population of pregnant women attending ANC at the same health facilities, HIV prevalence estimates may shift over time, and we were unable to control for any potential longitudinal effects in this analysis. However, the magnitude of difference in HIV prevalence observed between these two datasets is larger than one would expect to see at the same facility or in the same state in a one-year period, and does not appear to follow any pattern suggestive of a historical trend.

Objective 2: *Estimate LGA-level HIV prevalence among pregnant women attending ANC at PEPFAR-supported PMTCT sites in Nigeria in 2015.*

This analysis documents how PMTCT program data can be used to estimate local (LGA-level) HIV prevalence estimates that provide the granularity needed for HIV program planning and resource prioritization. The LGA HIV prevalence estimates generated through this analysis were used as the basis of PEPFAR's country operational planning for fiscal year 2017 to drive LGA prioritization and target-setting. Use of LGA-level HIV estimates – rather than state-level HIV prevalence estimates – is most crucial in the 23 states with statistically significant differences in LGA HIV prevalence (Table 3-5). These states – particularly the highest prevalence among them – should be prioritized for future survey and surveillance investments, and HIV surveys in these states should be

powered to detect and characterize sub-state differences in the burden of HIV. State-level HIV prevalence estimates may be adequate for the 14 states with minimal variation in within-state HIV prevalence.

Given the large sample size of pregnant women tested through PMTCT program data (2.2 million), we would expect the LGA HIV prevalence estimates produced through this analysis to be highly precise compared to other available HIV prevalence estimates. These LGA HIV prevalence estimates should have high discrimination, which is important given that the ability to rank and prioritize LGAs is critical for program planning purposes. However, it is important to note that these estimates have not been calibrated to the general population prevalence and reflect a sample (pregnant women attending ANC at PEPFAR-supported sites) with known biases. An estimated 61% of Nigerian women received antenatal care services at least once during their last pregnancy.[35,36] However, uptake of antenatal care services varies widely between states, from an estimated low of <18% to a high of >98%.[36] Therefore, in some states, the population of pregnant women attending antenatal care may differ from the population of pregnant women not accessing antenatal care services, thus introducing potential for selection bias. The HIV prevalence of pregnant women tested at antenatal care may differ from the HIV prevalence of the full population of pregnant women in a given LGA or state. Additionally, the population of pregnant women attending antenatal care in PEPFAR-supported facilities may or may not be representative of the population of pregnant women attending antenatal care at facilities not supported by PEPFAR.

The most significant limitations of this analysis are related to the use of programmatic data. PMTCT program data may be more imperfect and less rigorously collected and cleaned than research-quality data. The fiscal year 2015 PEPFAR PMTCT program data for Nigeria showed that a significant proportion (roughly 26%) of health facilities in some states reported numerators for HIV testing (number of pregnant women tested for HIV) that were larger than the reported denominators from which they were drawn (number of pregnant women attending antenatal care). This is due in many cases to results from pregnant women reached through large-scale HIV testing campaigns offered outside of health facilities being added to HIV testing registers at ANC sites. The *Methods* section describes in detail the weighting and exclusion criteria used to address these data quality concerns. While there are several potential sources of bias, we would expect the large sample size of PMTCT program data to account for random error, which may be more prevalent in routinely-collected program data compared to sentinel surveillance or survey data. Importantly, PEPFAR's support for PMTCT sites is not equal across or within states, so the ability to describe LGA HIV prevalence or the variability within states with few PMTCT sites is severely limited in some LGAs and states. In particular, LGA-level HIV prevalence estimates generated for Borno, Sokoto, and Yobe states are not robust given the limited data available from PEPFAR-supported PMTCT sites.

Overall conclusions & recommendations

Having accurate, reliable, and regularly-released descriptive epidemiologic data allows public health program officials to recognize epidemiologic patterns at the local levels, and direct limited resources accordingly. National surveys and periodic surveillance afford neither the granularity of descriptive data nor the frequency of results needed to support data-driven decision-making, and are expensive to conduct. Without LGA-level estimates, it would be difficult to direct resources within high burden states to where they are most needed. This analysis is innovative in that it represents the first use of PMTCT program data to describe the distribution of LGA-level HIV prevalence within states in Nigeria. This use of routinely collected programmatic data provides an exponential increase in the granularity of descriptive epidemiologic data, allowing for more precise targeting of interventions, without additional cost for data collection. Survey data will continue to play a critical role in calibrating estimates based on routine program data, but as the quality, reliability, and completeness of routine PMTCT program data improves, the need for regular ANC sentinel surveillance data on HIV prevalence will diminish.[37] Public health programs already invest a tremendous amount of resources into monitoring, evaluation, and reporting. Ensuring adequate resources are devoted to improved registers, enhanced and expanded electronic data systems including district health information systems, and dedicated data specialists at the facility, district, and state-levels is critical to producing high quality program data. This will allow routine data to be used for epidemiologic analyses that can help to refine

targeting of interventions, ensure programs are maximally effective, and optimize the impact of every dollar invested in public health programs.

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Chapter 4 : Assessing the association between facility-level factors and maternal and infant HIV outcomes in Malawi

ABSTRACT

Background.

Malawi pioneered the Option B+ (treat all) approach to prevention of mother-to-child transmission of HIV (PMTCT) in 2011. In 2012, Malawi's Ministry of Health launched a prospective cohort study called the National Evaluation of Malawi's PMTCT Program (NEMAPP) to evaluate the impact of the Option B+ program on mothers and infants. The objective of this analysis is to determine which facility-level variables contribute most significantly to improved health outcomes for mothers and infants.

Methods.

NEMAPP enrollment data from 2014-2016 (n=3,489 HIV positive mothers and HIV-exposed infants) was used together with facility staffing data and facility-aggregated routine PMTCT program data from Malawi's national PMTCT program for this analysis. Three-level mixed effects logistic regression models with random intercepts at district and facility levels were used to assess the associations between 7 facility-level and 5 individual-level variables on two outcomes: (1) exposed infant HIV status at six weeks postpartum, and (2) maternal use of ART during pregnancy. All analyses were stratified by whether mother-baby pairs (A) attended all antenatal (ANC), postnatal (PNC), and well child care at the same facility (n=2,745), or (B) sought care at multiple facilities (n=744).

Results.

A total of 163 (4.7%) infants tested positive for HIV at 6 weeks postpartum and 3,046 (87.7%) mothers were on ART during pregnancy. Among mother-baby pairs attending the same site consistently, receiving services at a public health facility versus a faith-based site was the most significant risk factor for infants testing positive for HIV at 6 weeks postpartum (OR: 4.6, 95% CI: [1.2 – 18.0]), and for mothers not being on ART (OR: 0.5, 95% CI: [0.2, 0.9]). Mothers traveling more than two hours to reach the clinic (OR: 2.7, 95% CI: [1.3 – 6.0]), mothers at sites with a high proportion of newly diagnosed HIV positive mothers (OR: 2.0, 95% CI: [1.4, 2.9]), and mothers at sites with a high provider to patient ratio (OR: 2.8, 95% CI: [1.7 – 4.5]) were significantly more likely to be on ART during pregnancy.

Discussion.

Facility-level risk factors identified through this analysis can be intervened on to improve maternal and infant HIV outcomes in Malawi's PMTCT program.

BACKGROUND & INTRODUCTION

In 2015, Malawi's HIV prevalence was 12.4% among women of childbearing age[1], and UNAIDS estimates that 4,800 infants were newly infected with HIV through mother-to-child transmission.[2] This figure represents a 71% decline in annual pediatric HIV infections since 2009.[2,3] This tremendous progress is credited largely to Malawi's leadership in developing and bringing to scale a public health approach to the prevention of mother-to-child transmission (PMTCT): immediate and lifelong antiretroviral therapy for all pregnant and breastfeeding women living with HIV, regardless of disease progression. Launched in 2011, this approach to PMTCT, called "Option B+" marked an important departure from the 2010 World Health Organization (WHO) guidelines, which recommended the use of one of two prophylactic antiretroviral medication regimens for pregnant and breastfeeding women with CD4 cell counts below 350 cells/mm^3.[4] Following Malawi's successful implementation of Option B+, WHO guidelines now recommend this approach for all countries.[5]

The scale-up of PMTCT services and roll-out of Option B+ across the highest burden countries in Sub-Saharan Africa corresponded with a 60% reduction in the number of new pediatric HIV infections between 2009 and 2015.[3] However, despite this progress, 110,000 children were newly infected with HIV in 2015 in the highest burden countries,[3] and mother-to-child transmission of HIV continues to present a significant public health threat. Furthermore, HIV/AIDS remains among the leading causes of death among women of childbearing age globally,[6] and without ART, mothers living with HIV are eight

times more likely to die in pregnancy and childbirth than their HIV uninfected counterparts.[7] Identifying ways to optimize PMTCT programs to improve health outcomes for mothers living with HIV and their children remains critically important.

While individual- and community-level factors contributing to maternal and infant HIV outcomes in PMTCT programs have been extensively studied,[8–20] less is known about how health facility-level factors may influence individual patient outcomes. Public health programs are in many cases better poised to intervene at the facility level than to attempt to change individual-level determinants of health outcomes. The objective of this analysis is to determine the association between health facility-level factors and maternal and infant HIV outcomes in Malawi's national PMTCT program.

We hypothesize that several key facility-level factors will significantly impact maternal and infant HIV outcomes, with attendance at public sector sites with a high volume of patients, a low volume of HIV positive patients, a low clinic staff-to-patient ratio, a high proportion of newly diagnosed HIV positive clients, a high proportion of mothers who have attended multiple sites for care during and after pregnancy, and rural location associated with poorer maternal and infant HIV outcomes. The scientific literature suggests that individual-level factors such as travel time and distance to the clinic, [8–15] maternal age,[10,12,14,16–21] parity,[8,10,19,22,23] and facility-based delivery[14,21] are also associated with maternal and infant outcomes, and we will assess these in our analyses as well.

METHODS

Data Sources & Creation of Analytic Dataset

Our analytic dataset comprises data from three sources: (1) the National Evaluation of Malawi's PMTCT Program (NEMAPP), (2) health facility staffing data collected during routine quarterly Ministry of Health site supervision visits, and (3) routinely collected health facility aggregated PMTCT program data from Malawi's national PMTCT program. Details on each of these are provided below.

National Evaluation of Malawi's PMTCT Program (NEMAPP) Data

The National Evaluation of Malawi's PMTCT Program (NEMAPP) is a nationally-representative prospective cohort study designed to evaluate the impact of the national Option B+ PMTCT program on HIV positive mothers and HIV-exposed infants. The evaluation was launched in September 2013 and is ongoing, with an expected completion date of March 2018. NEMAPP data are owned by Malawi's Ministry of Health, and this analysis is part of a first round of interim analyses using data from mother-baby pairs that were screened and enrolled in NEMAPP. The NEMAPP study design is as follows: first, investigators divided the country into four geographical areas (strata). Next, a two-stage sampling strategy using probability proportional to size (PPS) methods was used to randomly select (1) districts, and (2) health facilities for inclusion in the study. The sampling strategy is summarized in Figure 4-1.

Individual-level exposure and outcome data were collected for mother-baby pairs through a series of questionnaires administered at screening, enrollment, and follow-up visits. The full NEMAPP study protocol is included as an appendix. The number of mother-baby pairs included in NEMAPP screening, enrollment, and the analytic dataset are summarized in Figure 4-2. Pregnant women at 53 well child clinic sites were screened using the screening questionnaire. 3,553 HIV positive mothers and their HIV-exposed infants were enrolled in the NEMAPP study between 2014 and 2016 and completed an enrollment questionnaire. These mother-baby pairs will be followed prospectively for 24 months postpartum, with follow-up questionnaires administered at quarterly visits. A subset of 1,300 mother-baby pairs will be followed through 48 months postpartum, with quarterly follow-up visits. The analytic dataset includes data from enrollment for the 3,489 HIV positive mothers and their HIV-exposed infants who had complete data for ANC site attended and at least one outcome of interest (early infant diagnosis and maternal ART during pregnancy).

Figure 4-1: Stratified cluster randomized two-stage probability proportional to size (PPS) sampling design for the National Evaluation of Malawi's PMTCT Program (NEMAPP)

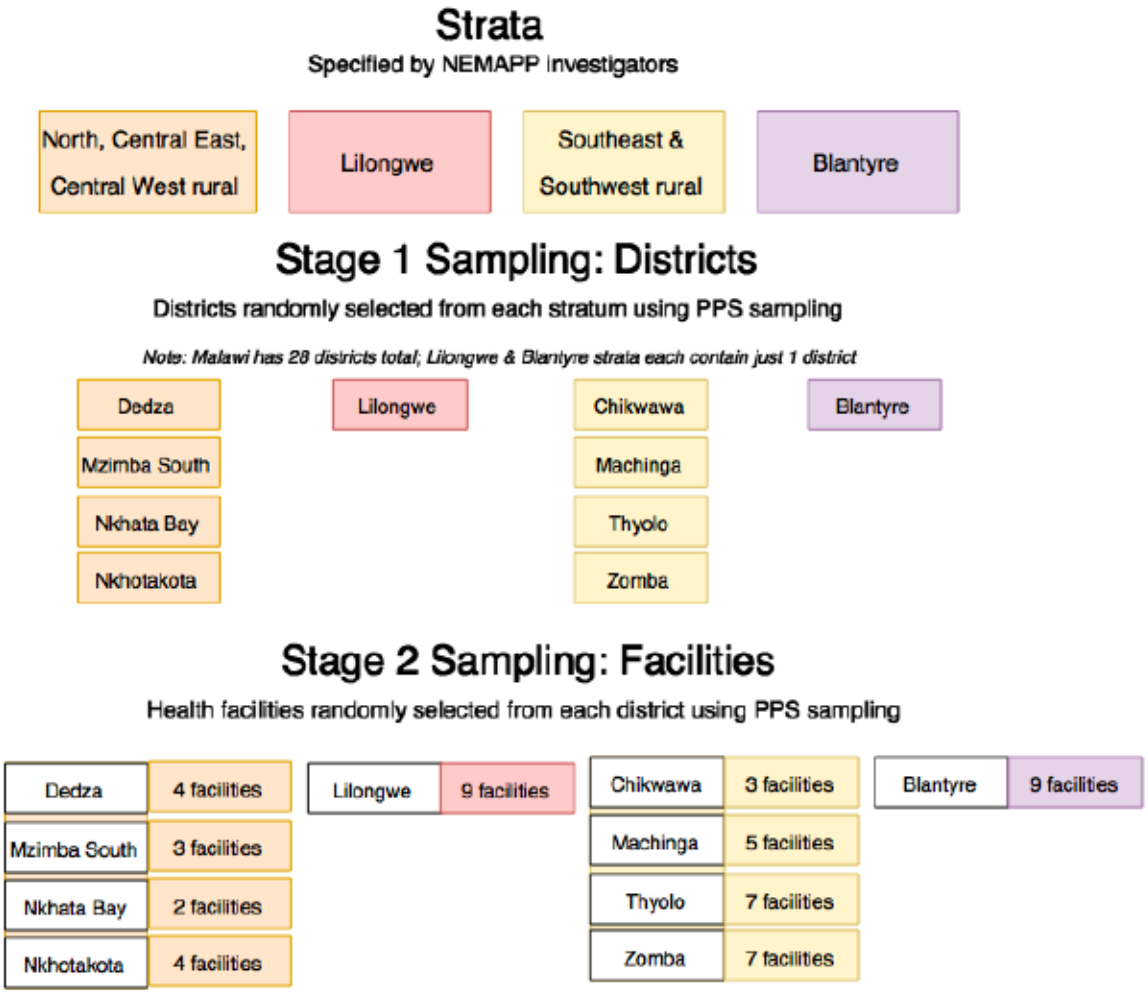
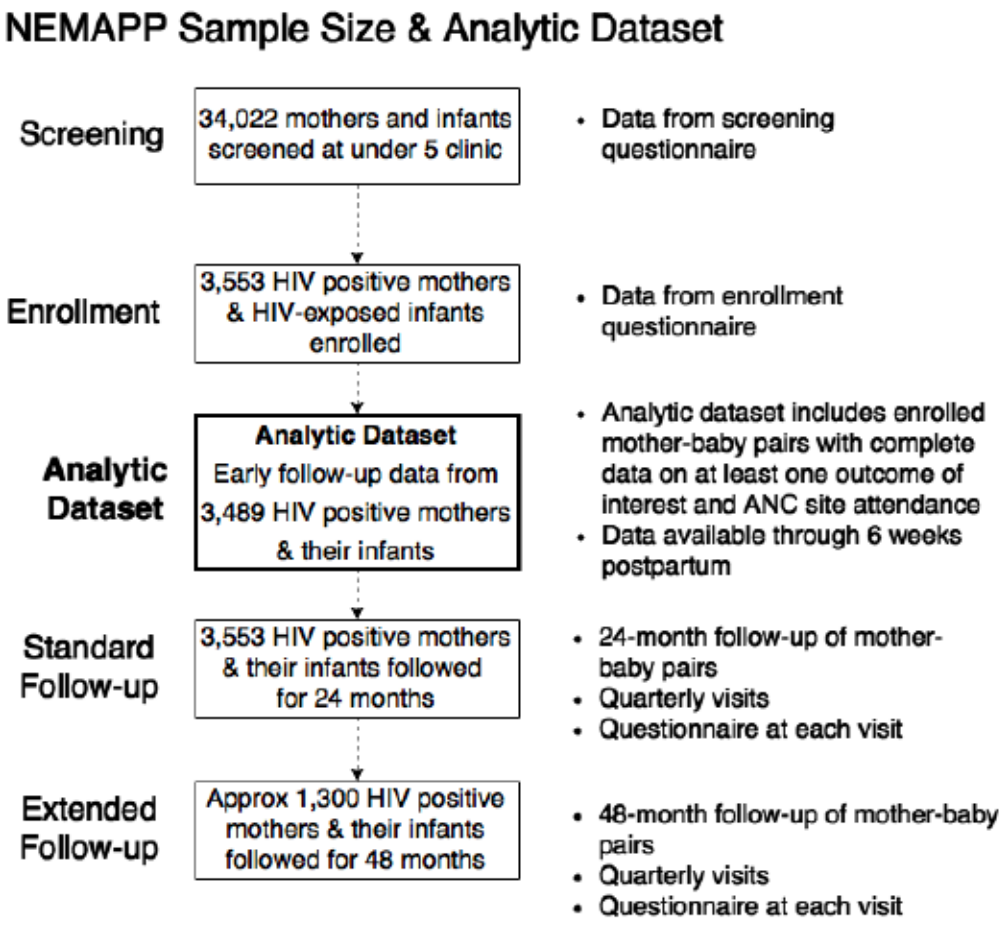


Figure 4-2: Sampling in National Evaluation of Malawi's PMTCT Program (NEMAPP)



Health facility staffing data

Malawi's Ministry of Health (MOH) conducts quarterly supportive supervisory visits to all health facilities supporting HIV care and treatment services.[24] One data element collected during these visits is the number of health facility staff present during the quarterly MOH site supervision visit in each of five cadres: auxiliary staff, nurses, clinicians, laboratory staff, and other staff. These staffing data were included in the analytic dataset in the form of a series of indicators reflecting the average (mean) number of staff in each cadre present at the site over four quarters from the middle of

the NEMAPP enrollment period (Q3 2015 – Q2 2016). Laboratory staff were not present at most facilities, so were excluded from the analytic dataset. The average number of nurses and clinicians was added together for each facility given that Malawi's task shifting policy allows both nurses and doctors to prescribe and administer antiretroviral therapy. We conducted a sensitivity analysis to explore whether including nurses and clinicians stratified by cadre rather than combined would change the results of univariate regression analyses and found that the results were not significantly different (analysis not shown). The combined nurse and clinician value was used to calculate an average provider to patient ratio at each facility.

Routine PMTCT program data

Malawi's MOH publishes facility-aggregated results from the national PMTCT program to their website on a quarterly basis. The analytic dataset includes site-aggregated data on patient volume (defined as the number of patients attending antenatal care (ANC), the number of HIV positive pregnant women per site, and the number of people living with HIV newly diagnosed vs. known positive prior to this pregnancy. These program data were used to calculate the average (mean) monthly value of patient volume and HIV positive patient volume at each facility over the same 12-month period (Q3 2015 – Q2 2016) used for extraction of facility staffing data. Similarly, the program data were used to calculate an average ratio of newly diagnosed to known positive PMTCT clients at each health facility.

Variables

This analysis includes three individual-level dependent variables and a series of facility-level and individual-level independent variables. Maternal and infant HIV outcomes of interest, facility-level covariates of interest, and individual-level covariates of interest and the associated data source for each indicator are listed in Table 4-1.

Table 4-1: Variables of interest

Variables	Data source
Level 1 (individual-level) maternal & infant outcomes	
1. HIV status of infants born to HIV positive mothers at 6 weeks postpartum	NEMAPP
2. HIV positive mother was on antiretroviral therapy (ART) during pregnancy	NEMAPP
Level 2 (facility-level) covariates	
1. Average monthly volume (#) of patients at the health facility	Routine MOH program data
2. Average monthly volume (#) of HIV positive patients at the health facility	Routine MOH program data
3. Ratio of newly identified to known HIV positive clients	Routine MOH program data
4. Provider-to-patient ratio (nurses & doctors)	MOH staffing data & Routine MOH program data
5. Location (urban, boma (peri-urban), rural)	NEMAPP
6. Type of facility (public, mission)	NEMAPP
7. Proportion of study participants who attended both antenatal and postnatal care services at the site	NEMAPP
Level 1 (individual-level) covariates	
1. Time spent traveling to clinic	NEMAPP
2. Mother attended ANC and PNC services at the same facility	NEMAPP
3. Mother is young (<25 years old)	NEMAPP
4. Mother delivered child in a health facility	NEMAPP
5. Parity (1st, 2nd, 3, 4+ pregnancy)	NEMAPP

Analytic Methods

Statistical analyses

Exploratory data analyses including boxplots and tables were used to characterize the distribution of variables, and missingness was assessed in variables of interest. The

analytic dataset was restricted to include only mother-baby pairs with complete data for (a) the outcome of interest for each analysis, and (b) whether the mother attended the same site or multiple sites for ANC, PNC, and well-baby care services (2% missing, see Figure 4-2). Within the analytic dataset, there was minor missingness for each of the two outcome variables and two independent variables. In brief, data were missing as follows: infant HIV status at 6 weeks postpartum (1% missing); whether the mother was on ART during pregnancy (1% missing); time spent traveling to the clinic (3% missing), and whether the infant was delivered in a health facility (3% missing). Table 4-2 summarizes missingness within the analytic dataset, stratified by whether the mother changed sites between ANC, PNC, and well child care. Given the minor degree of missingness (96% of records in the analytic dataset were complete for all variables of interest), and the fact that the pattern of missingness was approximately equivalent between the two strata, we used complete data for this analysis.

Table 4-2: Summary of missingness in analytic dataset, stratified by whether mother changed sites between ANC, PNC, and well child care

	Mothers who changed sites (n=744)	Mothers who did not change sites (n=2,745)
Variable	Missing n (%)	Missing n (%)
Infant HIV status (DNA-PCR result at 6 weeks postpartum)	3 (0.4%)	28 (1.0%)
Mother was on ART during pregnancy	2 (0.3%)	14 (0.5%)
Time spent traveling to the clinic from home	25 (3.5%)	74 (2.7%)
Child was born in a health facility	24 (3.5%)	64 (2.3%)

Three-level mixed effects logistic regression models with robust standard errors were fit for each of the two outcomes, stratified by whether the mother attended all ANC, PNC, and well child care at the same facility. The models included random intercepts at the district and health facility levels to account for patients clustering within health facility and health facilities clustering within district. Probability weights were included at the district, facility, and individual levels to account for the survey design and sampling structure of the NEMAPP data. For each of the two outcomes, we ran unadjusted models with each facility-level and patient-level covariate of interest as a main term, as well as a fully adjusted model that included main terms for all covariates of interest. We then added covariates to the unadjusted models one by one, comparing results to assess potential confounding and statistical interaction. Akaike's information criteria (AIC) was used for model selection. We conducted stratified regression analyses for each of the two outcomes, based on whether mothers attended all ANC, PNC, and well child care at the same site. Facility-level variables and random effects are associated with the study site where the mother-baby pair attended well child care and was enrolled in NEMAPP. Statistical significance was defined as alpha < 0.05. All analyses were completed using StataMP 2 cores, version 14.2[25].

RESULTS

The analytic dataset contains data on 3,489 HIV positive mothers and their infants. Overall, 4.7% of infants tested positive for HIV at 6 weeks postpartum, and 87.7% of HIV positive mothers were on ART during pregnancy. Most mother-baby pairs consistently attended the same facility for receipt of ANC, PNC, and well child services (79%,

n=2,745), but some mothers changed sites between ANC, PNC, and well child services (21%, n=744). Table 4-3 provides descriptive statistics of the study population in total, and stratified by whether the mother-baby pair attended the same site consistently or changed sites during the pregnancy or postpartum period.

Table 4-3: Description of the study population included in analytic dataset

Variable	n	Mother attended same site for ANC and well child care (n=2,745) Prop.	Mother changed sites between ANC and well child care (n=744) Prop.	Total (n=3,489) Prop.
Level 1 (individual-level) outcomes				
Positive infant HIV status (positive DNA-PCR result at 6 weeks postpartum) (n=3,458)	163	0.05	0.05	0.05
Mother was on ART during pregnancy (n=3,473)	3,046	0.89	0.81	0.88
Level 2 (facility-level) variables				
Average monthly patient volume (n=3,489)				
<100	762	0.19	0.33	0.22
100-199	1,241	0.37	0.31	0.36
200-299	683	0.20	0.16	0.20
300-399	419	0.11	0.14	0.12
400+	384	0.12	0.06	0.11
Average monthly volume of HIV+ patients at facility, categorical (n=3,489)				
<10	1,435	0.39	0.50	0.41
10-19	665	0.20	0.15	0.19
20-29	566	0.17	0.14	0.16
30-39	316	0.08	0.13	0.09
40+	507	0.16	0.08	0.15
Average monthly ratio of newly identified HIV+ patients to known HIV+ positive (n=3,489)				
Mean, (std dev)	3,489	1.18, (0.66)	1.19, (0.69)	1.18, (0.67)
Study site is public sector facility (compared to mission / faith-based) (n=3,489)	2,949	0.87	0.74	0.85

Study site is urban, boma (peri-urban), or rural (n=3,489)				
Urban	1,242	0.35	0.38	0.36
Boma (peri-urban)	499	0.16	0.10	0.14
Rural	1,748	0.50	0.52	0.50
Average ratio of ART prescribers (nurses or doctors) to patients at site (n=3,489);				
Mean, (std dev)	3,489	0.17, (0.18)	0.23, (0.26)	0.18, (0.20)
Average proportion of mothers at the study site attending all ANC, PNC, and well child visits at the same site (n=3,489)				
Mean, (std dev)	3,489	0.81, (0.12)	0.70, (0.16)	0.79, (0.14)
Level 1 (individual-level) variables				
Time spent traveling to the clinic from home (n=3,390)				
<1 hour	1,546	0.46	0.44	0.46
1-2 hours	1,274	0.38	0.36	0.38
>2 hours	570	0.16	0.20	0.17
Parity: third or greater child (n=3,489)	1,149	0.32	0.37	0.33
Child was born in a health facility (n=3,401)	3,224	0.95	0.95	0.95
Mother's age < 25 years (n=3,489)	920	0.25	0.31	0.26

Several facility-level factors differ by type of facility (mission or faith-based compared to public), and this is summarized in Table 4-4. Most notably, compared to mission facilities, public sites tend to have higher overall patient volume, a higher volume of HIV positive clients, a higher proportion of mothers who attend all ANC, PNC, and well child services at the same site, are more often located in urban areas, and have a lower provider to patient ratio with more doctors but fewer nurses on site. Client characteristics were similar at the two types of facilities, but public sites have a slightly higher proportion of mothers with first or second-born children.

Table 4-4: Site and client characteristics by facility type (mission or faith-based compared to public facilities) in Malawi

Variables	Mission Facilities (n=9 sites)	Public Facilities (n=45 sites)
Average monthly volume of patients at ANC	122.32	223.60
Average monthly volume of HIV+ pregnant women at ANC	8.78	21.06
Proportion of clients attending all ANC, PNC, and well child services at same site	0.65	0.81
Proportion of sites located in urban areas	0.17	0.39
Average monthly provider to patient ratio	0.24	0.17
Average number of doctors on site	4.31	6.71
Average number of nurses on site	15.80	14.45
Proportion of clients with facility-based delivery	0.93	0.95
Proportion of mothers at site <25 years old	0.24	0.27
Proportion of mothers at site traveling <1 hour to clinic	0.45	0.46
Proportion of mothers at site for whom child is 1st or 2nd born	0.29	0.34

Outcome 1: HIV-exposed infant HIV status at 6 weeks postpartum

Univariate associations for each variable of interest with HIV-exposed infant status in the unstratified analytic dataset are summarized in Table 4-5. The following variables yielded a statistically significantly increased odds of HIV-exposed infants testing positive at 6 weeks postpartum: attending a public health facility, compared to faith-based (OR: 3.73, 95% CI: [1.67, 8.32]), attending a site with an average monthly patient volume of 300-399 (OR: 2.52, 95% CI: [1.31, 4,84]), attending a site with an average monthly volume of HIV positive pregnant women of 30-39 (OR: 1.57, 95% CI: [1.01, 2.43]), or greater than 40 (OR: 2.24, 95% CI: [1.04, 4.82]), maternal age less than 25 years old (OR: 1.65, 95% CI: [1.20, 2.26]), and parity (child is mother's first or second-born) (OR: 2.06, 95% CI:[1.09, 3.87]). In unadjusted multilevel regression analyses, attending a clinic in a

rural location was found to have a statistically significant protective effect against infants testing positive for HIV at 6 weeks postpartum (OR: 0.61, 95% CI: [0.46, 0.80]).

Table 4-5 : Univariate associations between variables of interest and outcome 1: HIV-exposed infant HIV status at 6 weeks postpartum

Variable	Odds Ratio	p-value	95% Confidence Interval	
Level 2 (facility-level) variables				
Average monthly patient volume (ref: <100)				
100-199	1.01	0.98	0.36	2.81
200-299	1.86	0.16	0.79	4.42
300-399	2.52	0.01	1.31	4.84
400+	1.38	0.32	0.73	2.62
Average monthly HIV positive patient volume (ref: <10)				
10-19	1.43	0.56	0.43	4.72
20-29	1.44	0.39	0.63	3.28
30-39	1.57	0.04	1.01	2.43
40+	2.24	0.04	1.04	4.82
Ratio of newly identified to known positive patients	1.25	0.08	0.97	1.61
Clinic is urban, boma (peri-urban), or rural (ref: urban)				
Boma (peri-urban)	1.41	0.46	0.57	3.49
Rural	0.61	0.00	0.46	0.80
Nurse & doctor to patient ratio	1.04	0.93	0.43	2.50
Site is public facility (ref.: faith-based)	3.73	<0.01	1.67	8.32
Average proportion of mothers at the study site attending all ANC, PNC, and well child visits at the same site	1.09	0.93	0.14	8.66
Level 1 (individual-level) variables				
Mother attended same site for ANC, PNC, & well child care	0.78	0.51	0.38	1.63
Travel time to clinic (ref.: <1 hour)				
1-2 hours	0.95	0.79	0.65	1.38
>2 hours	0.90	0.82	0.35	2.27
Mother is <25 years of age	1.65	0.02	1.20	2.26
Child is mother's 1st or 2nd born (ref: 3rd +)	2.06	0.03	1.09	3.87
Mother delivered child in health facility (ref: no)	0.65	0.31	0.28	1.50

Adjusted regression results differed by whether the mother attended the entirety of her ANC, PNC, and well child services at the study site, or whether she attended some or all ANC visits at another clinic. Adding a statistical interaction term between this variable and the facility's patient-provider ratio to the adjusted model improved the model fit as measured by AIC, but the interaction term was not statistically significant (p=0.09), so it was not included in the model. However, other variables were noted to change significantly depending on whether the mother received all ANC and PNC care at the study site or not, so adjusted results were stratified by whether the mother received all ANC, PNC, and well child services at the same site.

The final model for infant HIV status at 6 weeks postpartum included the mother's travel time to the clinic, the ratio of newly identified to known positive patients at the site, the provider to patient ratio, the facility type (public vs faith-based), whether the child was delivered in a health facility, and parity. Results were stratified by whether the mother received all ANC, PNC, and well child services at the study site, and are summarized in Table 4-6.

In the adjusted regression model, among women attending all ANC and PNC services at the study site (n=2,743), the type of facility (public facility vs. faith-based or mission facility) was strongly associated with exposed-infant HIV status at 6 weeks postpartum in Malawi. HIV positive mothers seeking ANC, PMTCT, PNC, and well child services at public health facilities were significantly more likely to have an infant testing positive for

HIV at 6 weeks postpartum (OR: 4.57, 95% CI: [1.16 – 18.02]). Other facility- and individual-level factors were also associated with a change in the odd of infants testing positive for HIV at 6 weeks postpartum, but these associations were not statistically significant. Specifically, seeking care at facilities with a high ratio of new to known HIV positive clients, and mothers experiencing their first or second pregnancies (compared to third or higher) were associated with an increased odds of infants testing positive for HIV. Traveling more than one hour to reach the clinic, sites with a high patient to provider ratio, and having a facility-based delivery were all associated with a decreased odds of infants testing positive for HIV.

In the adjusted regression model, among mothers attending some or all ANC services at a health facility other than the study site where she received postnatal services (n=767), the ratio of newly identified to known positive patients at the study site (OR: 1.93, 95% CI: [1.46 – 2.50]), the provider to patient ratio (OR: 3.87, 95% CI: [1.40 – 10.73]), and parity (this child being the mother's first or second-born vs. third or greater) (OR: 2.73, 95% CI: [1.47 – 5.05]) were all statistically significantly associated with an increased odds of the infant testing positive for HIV. While not statistically significant, traveling for more than one hour to reach the clinic, and the facility type (public vs faith-based) were also associated with an increased odds of infants testing positive for HIV at six weeks postpartum, while delivering the child in a health facility was associated with a decreased odds of infants testing positive for HIV. Results are summarized in Table 4-6.

Table 4-6: Adjusted multilevel regression results for outcome 1: infant HIV status at 6 weeks postpartum, stratified by whether mothers received all ANC, PNC, and well child care in same site

	Mothers receiving all ANC, PNC, and well child care in same site		Mothers receiving ANC, PNC, and well child care in 2 or more sites	
Variable	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Level 2 (facility-level) variables				
Ratio of newly identified to known positive patients	1.20 (0.96, 1.51)	0.11	1.93 (1.49, 2.50)	<0.01
Nurse & doctor to patient ratio	0.31 (0.07, 1.37)	0.12	3.87 (1.40, 10.73)	0.01
Site is public facility (ref.: faith-based)	4.57 (1.16, 18.02)	0.03	2.51 (0.95, 6.64)	0.06
Level 1 (individual-level) variables				
Travel time to clinic (ref.: <1 hour)				
1-2 hours	0.89 (0.52, 1.51)	0.65	1.79 (0.93, 3.43)	0.08
>2 hours	0.84 (0.38, 1.88)	0.67	2.38 (0.31, 18.18)	0.40
Mother delivered child in health facility	0.63 (0.25, 1.60)	0.33	0.56 (0.06, 5.55)	0.62
Child is mother's 1st or 2nd born (ref: 3rd +)	1.71 (0.64, 4.59)	0.29	2.73 (1.47, 5.05)	<0.01
Random Effects				
Variance at district level	0.35 (0.09, 1.34)		0.23 (0.08, 0.69)	
Variance at facility level	0.34 (0.11, 1.04)		<0.01 (<0.01, <0.01)	
Akaike's Information Criteria	**AIC: 7,908.32**		**AIC: 2,722.26**	

Outcome 2: Maternal ART during pregnancy

Univariate associations for each variable of interest in the unstratified analytic dataset are summarized in Table 4-7. The following variables were statistically significantly associated with a decreased odds of mothers being on ART during pregnancy: attending a high volume site with an average monthly patient volume of 400 or more pregnant women in ANC (OR: 0.35, 95% CI: [0.24, 0.51]), attending a site with on average 30-39 HIV positive pregnant women at ANC each month (OR: 0.29, 95% CI: [0.23, 0.34]),

attending a public health facility (compared to mission or faith-based) (OR: 0.32, 95% CI: [0.15, 0.70]), mother is less than 25 years old (OR: 0.31, 95% CI: [0.18, 0.52]), and parity (child is mother's first or second born) (OR: 0.38, 95% CI: [0.28, 0.52]). Rural facility location (OR: 1.98, 95% CI: [1.56, 2.52]) and attending the same site consistently for ANC, PNC, and well child care (OR: 2.26, 95% CI: [1.59, 3.23]) were statistically significantly associated with an increased odds of HIV positive mothers being on ART while pregnant in the unadjusted analysis.

Table 4-7 : Univariate associations between variables of interest and outcome 2: maternal ART during pregnancy

Variable	Odds Ratio	p-value	95% Confidence Interval	
Level 2 (facility-level) variables				
Average monthly patient volume (ref: <100)				
100-199	0.86	0.57	0.51	1.45
200-299	0.82	0.43	0.51	1.33
300-399	0.62	0.41	0.20	1,94
400+	0.35	<0.01	0.24	0.51
Average monthly HIV positive patient volume (ref: <10)				
10-19	0.75	0.38	0.39	1.44
20-29	0.76	0.39	0.41	1.41
30-39	0.29	<0.01	0.23	0.34
40+	0.59	0.13	0.30	1.17
Ratio of newly identified to known positive patients	1.18	0.25	0.89	1.55
Clinic is urban, boma (peri-urban), or rural (ref: urban)				
Boma (peri-urban)	1.59	0.02	1.08	2.34
Rural	1.98	<0.01	1.56	2.52
Nurse & doctor to patient ratio	1.49	0.23	0.77	2.88
Site is public facility (ref.: faith-based)	0.32	<0.01	0.15	0.70
Average proportion of mothers at the study site attending all ANC, PNC, and well child visits at the same site	1.30	0.60	0.48	3.54
Level 1 (individual-level) variables				
Mother attended same site for ANC, PNC, & well child care	2.26	<0.01	1.59	3.23
Travel time to clinic (ref.: <1 hour)				

1-2 hours	1.15	0.53	0.74	1.80
>2 hours	1.76	0.06	0.99	3.13
Mother is <25 years of age	0.31	<0.01	0.18	0.52
Child is mother's 1st or 2nd born (ref: 3rd +)	0.38	<0.01	0.28	0.52
Mother delivered child in health facility (ref: no)	1.13	0.66	0.66	1.93

The final model for maternal ART included the ratio of newly identified to known positive patients at the site, the travel time to the clinic, the type of site (public vs. faith-based), the site's provider to patient ratio, whether the mother is 25 years old or younger, whether the child was delivered in a health facility, and whether the child is the mother's first or second born. Adjusted results are stratified by whether the mother received all ANC, PNC, and well child services at the study site, and are summarized in Table 4-8.

Adjusted regression results among women attending all ANC and PNC services at the study site (n=2,767) showed that the facility's ratio of newly identified to known positive patients, traveling more than two hours to reach the clinic, the type of facility (public vs. faith-based), the facility's patient to provider ratio, and the mother's age were all significantly associated with maternal ART status during pregnancy after controlling for other factors. Patients at sites with a high ratio of newly identified vs. known HIV positive clients were significantly more likely to be on ART during pregnancy (OR: 2.03, 95% CI: [1.41 – 2.92]). Mothers traveling more than two hours to reach the clinic were significantly more likely to be on ART during pregnancy than those who traveled less than an hour (OR: 2.74, 95% CI: [1.25 – 6.00]). HIV positive mothers receiving care at public health facilities were significantly less likely to be on ART during pregnancy than

mothers attending faith-based facilities (OR: 0.47, 95% CI: [0.24 – 0.92]). Mothers at sites with a high provider to patient ratio were significantly more likely to be on ART during pregnancy than those attending sites with lower provider to patient ratios (OR: 2.78, 95% CI: [1.71 – 4.50]). Young mothers (25 years old or younger) were less likely to be on ART during pregnancy than older mothers (OR: 0.37, 95% CI: [0.14 – 1.00]), with borderline statistical significance. Delivering the child in a health facility was associated with a moderate but not statistically significant increased odds of being on ART during pregnancy, and while parity improved the overall model, it showed little effect on receipt of maternal ART during pregnancy.

Adjusted regression results for mothers who sought ANC and PNC services at more than one health facility (n=778) showed that the ratio of newly identified to known positive patients, the type of facility (public vs. faith-based), the mother's age, and parity were significantly associated with the odds that mothers living with HIV received ART during pregnancy. A higher facility ratio of newly identified to known positive patients significantly decreased the odds that mothers received ART during pregnancy (OR: 0.75, 95% CI [0.58, 0.96]). Women seeking care in public facilities were significantly less likely to receive ART during pregnancy (OR: 0.44, 95% CI: [0.26 – 0.76]). Young mothers (24 years old or younger) were significantly less likely to be on ART during pregnancy than older mothers (OR: 0.56, 95% CI: [0.37 – 0.84]). If the child was the mother's first or second born, the mother was significantly less likely to be on ART during pregnancy (OR: 0.41, 95% CI: [0.20 – 0.83]). Other variables were also associated with a decreased odds of maternal ART during pregnancy, though these relationships were not statistically

significant: traveling more than one hour to the clinic, the provider to patient ratio, and facility-based delivery.

Table 4-8: Adjusted multilevel regression results for outcome 2: maternal ART during pregnancy, stratified by whether mothers received all ANC, PNC, and well child care in the same site

	Mothers receiving all ANC, PNC, and well child care in same site		Mothers receiving ANC, PNC, and well child care in 2 or more sites	
Variable	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Level 2 (facility-level) variables				
Ratio of newly identified to known positive patients	2.03 (1.41, 2.92)	<0.01	0.75 (0.58, 0.96)	0.02
Nurse & doctor to patient ratio	2.78 (1.71, 4.50)	<0.01	0.91 (0.59, 1.43)	0.69
Site is public facility (ref.: faith-based)	0.47 (0.24, 0.92)	0.03	0.44 (0.26, 0.76)	<0.01
Level 1 (individual-level) variables				
Travel time to clinic (ref.: <1 hour)				
1-2 hours	1.14 (0.74, 1.74)	0.56	0.96 (0.35, 2.62)	0.93
>2 hours	2.74 (1.25, 6.00)	0.01	0.85 (0.35, 2.10)	0.73
Mother delivered child in health facility	1.54 (0.99, 2.41)	0.06	0.54 (0.12, 2.43)	0.42
Child is mother's 1st or 2nd born (ref: 3rd +)	1.02 (0.47, 2.21)	0.96	0.41 (0.20, 0.83)	0.01
Random Effects				
Variance at district level	0.35 (0.16, 0.74)		0.43 (0.09, 1.97)	
Variance at facility level	0.26 (0.10, 0.71)		<0.01 (<0.01, 1.35E+14)	
Akaike's Information Criteria	**AIC: 12,341.93**		**AIC: 6,305.79**	

DISCUSSION

This analysis highlights the importance of several key facility-level and individual-level factors in determining maternal and infant health outcomes among PMTCT clients in Malawi. Among women attending the same site throughout ANC, PNC, and well child

care, attending a public health facility was the most significant risk factor associated for having an infant test positive for HIV at 6 weeks postpartum and for the mother not being on ART during her pregnancy. Attending sites with a high provider to patient ratio, a high proportion of pregnant women newly identified as HIV positive, and traveling for more than two hours to reach a site were all significantly associated with an increased odds of these mothers being on ART during pregnancy. Among women changing facilities between ANC, PNC, and well child care, those who received well child care at sites with a high provider to patient ratio, a high proportion of pregnant women newly identified as HIV positive, and those who were pregnant with a first or second child were significantly more likely to have infants testing positive for HIV at 6 weeks postpartum. Within this stratum, risk factors for not being on ART during pregnancy included attending a public health facility, attending a site with a high ratio of newly diagnosed HIV positive pregnant women, or being pregnant with a first or second-born child.

Seeking care at a public health facility emerged consistently as an important risk factor for both outcomes of interest in both strata. This is most likely explained in part by important differences in other variables at public versus mission or faith-based facilities (see Table 4-4, which summarizes these differences by site type). While the adjusted models controlled for many of these factors separately, several variables including patient volume, volume of HIV positive patients, and urban versus rural location were mild to moderate predictors of outcomes in the univariate analyses but were excluded

from the adjusted analyses as their inclusion did not improve the predictive power of the models. Disparities in these measured variables may partially explain differences in outcomes seen for women attending the two types of facilities, but there may be other important unmeasured differences between these facility types, and this merits further exploration.

The multilevel nature of this analysis allows us to understand the interplay between facility-level factors and individual-level factors that influence the likelihood of mothers receiving ART during pregnancy and preventing early transmission of HIV to their infants. The facility-level factors identified as being the most critical predictors of maternal and infant outcomes in this analysis (facility type, provider to patient ratio, and ratio of newly diagnosed versus known positive pregnant women) should be prioritized by Ministry of Health and HIV/AIDS partners for programmatic intervention. Ensuring an adequate and appropriate clinical staffing footprint at each health facility is critical to protecting the health of mothers and children, and this finding is consistent with other studies.[14,26,27] Improving the staff to patient ratio at PMTCT sites may require a redistribution of human resources for health across facilities, an absolute increase in the number of nurses and doctors employed at these sites, or a combination of both. In particular, sites with a high proportion of newly diagnosed pregnant mothers may require additional staffing for counseling, peer mothers, or other resources to ensure that these mothers are able to successfully initiate and adhere to their new ART regimen.[14] Individual level factors found to be important predictors of maternal and

infant outcomes (travel time to the clinic, maternal age, and parity) ought to inform how PMTCT programs target individuals who may be at higher risk for poor uptake of or adherence to maternal ART and vertical transmission of the virus.

Time spent traveling to the clinic seemed to have a mixed effect; longer travel time was associated with an increased likelihood of infants testing positive for HIV, but mothers being more likely to be on ART during pregnancy. Studies have shown that traveling a long distance is associated with a decreased likelihood of regular ANC attendance,[8,9] and poorer adherence to ART among pregnant women.[12,14,28] One possible explanation for our finding is that mothers living far from the clinic must exhibit strong health seeking behavior in order to travel such a long distance to access services, and they may be more likely to initiate ART during pregnancy. However, given the long distance, consistently returning to the clinic to obtain ARV medications could be a challenge, and poor adherence would lead to increased potential for vertical transmission. For PMTCT clients who travel a long distance to reach the clinic, WHO recommends transportation vouchers or other assistance with defraying transportation costs.[5]

One unexpected outcome was that the nature and magnitude of the association between several variables and outcomes differed significantly depending on whether mothers received all ANC and PNC services at the study site, or whether they sought services at multiple clinics. For example, a high provider to patient ratio had a non-significant protective effect against infants testing positive for HIV at six weeks

postpartum within the full study population before stratification. The same association was observed among mothers attending all ANC and PNC services at the same site, but a high provider to patient ratio was shown to statistically significantly increase the odds of infants testing positive for HIV if their mothers sought services at more than one clinic. There are several possible explanations for this phenomenon. It may be that restricting the analytic population to include mother-baby pairs who received all care at the same site allowed for a truer assessment of how the facility-level factors at that site impacted maternal and infant outcomes. For example, if a mother received most or all of her antenatal care at another facility, the staffing footprint or other site-level factors at her well child care facility would not be expected to impact the likelihood that she was on ART during pregnancy. To that end, results from the stratum of women that changed health facilities between ANC, PNC, and well child care should be interpreted with caution. Secondly, it may be that certain measured and unmeasured facility-level factors drive some women to switch facilities mid-way through their pregnancies or immediately following delivery, such as perceived quality of care, how the nurses and doctors treat HIV positive pregnant women, or wait time at the clinic. If her ANC site had a low provider to patient ratio which resulted in poorer quality of care (and negative health outcomes), the mother may have intentionally relocated to a facility with better quality services (and a better provider to patient ratio) for postnatal care and well child services. This could explain why the direction of association for some variables is the opposite of what we would intuitively expect, such as the unexpected increase in infant positivity among mothers attending postnatal services at sites with a

higher provider to patient ratio. Finally, it is possible that the facility and individual-level risk factors for mother-baby pairs who are geographically stable and able to consistently seek care in the same facility truly differ from those for families who are more mobile, particularly if that mobility is driven by economic instability.

There are several important limitations to this analysis. Without information about the timing of transfer between health facilities or qualitative data explaining the reasons some women sought care at more than one site for ANC, PNC, and well child services, we may be pooling and analyzing a group of mother-baby pairs that really ought to be further stratified. For example, switching midway through ANC care may signal an issue with the mother's satisfaction with ANC care received thus far, while switching facilities after delivery could be motivated by something different entirely – perhaps she returned home to deliver and raise her baby. Importantly, as mentioned above, facility-level factors were measured for well child care sites where women were enrolled in NEMAPP, and if women received the bulk of their antenatal care at another health facility, conclusions drawn about facility-level associations with maternal and infant outcomes may not be correct for some women in this stratum. Additional data on ANC sites was collected for some women who attended multiple facilities, but not for all. Collecting this information more completely, together with data on when women moved between facilities would allow for an important follow-up analysis that may further illuminate the results presented here. Lastly, given that the analytic dataset contains only data from enrollment, we were limited to analyzing infant HIV status at 6

weeks postpartum. Later analyses of NEMAPP data will allow for longitudinal analyses of factors influencing transmission during the breastfeeding period, and additional maternal and infant health outcomes that will be tracked over time can be analyzed.

This analysis underlines the importance of understanding and intervening on key facility-level variables that significantly influence maternal and infant outcomes in Malawi's PMTCT program, and targeting interventions to patients with individual-level factors that elevate their risk for poor outcomes. This analysis should be repeated with NEMAPP data as mother-baby pairs are followed over time to determine whether facility-level factors influencing maternal and infant outcomes change over time or are consistent with those identified in this first analysis using early transmission data. In order to maximize the lifesaving potential of the Option B+ program, efforts to evaluate and intervene on facility and individual level factors that affect health outcomes for mothers and infants should continue to be prioritized.

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Chapter 5 : Summary and Conclusions

Summary of Key Findings

The three analyses presented in this dissertation highlight how routinely collected program data can be used to generate granular descriptive epidemiologic data needed for program management, and how routine data can be used in combination with research, evaluation, survey, or surveillance data to support multilevel analyses to diagnose issues in public health programs. In this chapter, we summarize key findings from this dissertation and discuss the implications of these findings for research and public health practice.

Summary of key findings for aims 1 and 2

Chapter 3 presented the analyses for the first two aims. The first aim (presented in this chapter as Objective 1) was to evaluate the difference between state and facility-level HIV prevalence measured through routine PMTCT program data at PEPFAR-supported sites in fiscal year 2015 compared to HIV prevalence measured at the same facilities through ANC sentinel surveillance (ANC-SS) in Nigeria in 2014. At the facility-level, we found significant differences in HIV prevalence estimates generated using PMTCT data compared to ANC-SS data. While the average difference in prevalence estimates between the two data sources was close to zero (mean: 0.11%, median -0.06%), this average value obscured large positive and negative differences at the facility level, ranging from -13.2% to 23.2%, and a large standard deviation and variance: 3.76% and

14.14%. In the context of a low prevalence epidemic like Nigeria's, where the national adult HIV prevalence is estimated at 3.1%,[1] differences of this magnitude between HIV prevalence estimates based on pregnant women tested at the same health facility are unacceptably large. Linear regression analysis was used to assess the extent to which variation between the estimates could be explained by other factors. We found that there was no statistically significant association between PMTCT program prevalence and urban/rural location, geographic location in the North versus South of the country, PEPFAR implementing partner, US Government agency supporting the site, or state HIV prevalence based on PMTCT program data. ANC-SS alone explains approximately 54.7% of variation in PMTCT program prevalence. An additional 15.8% of this variation was explained by total patient volume at the site, the volume of HIV positive patients at the site, and the statistical interaction between ANC-SS and HIV positive patient volume.

Analysis of the state-level HIV prevalence estimates based on ANC-SS (n=160 sites, approximately 36,000 pregnant women) compared to state-level estimates based on testing data from all PEPFAR-supported PMTCT sites (n=5,662 sites, approximately 2.2 million pregnant women) illuminated a clear pattern: in 29 of 37 states, the ANC-SS based prevalence estimates were higher than estimates based on PMTCT program data. On average, ANC-SS state HIV prevalence estimates were 1.8% higher than PMTCT data-based estimates (95% CI: [1.3%, 2.3%]). This suggests that the population of pregnant women tested through ANC-SS sites is likely not representative of the population of

pregnant women in each state, and ANC-SS may be systematically over-estimating the burden of HIV in Nigeria.

The second aim (presented in this chapter as Objective 2) was to estimate local government area (LGA)-level HIV prevalence among pregnant women attending antenatal care (ANC) services in PEPFAR-supported facilities in Nigeria in fiscal year 2015. Through this analysis we produced Empirical Bayes modeled HIV prevalence estimates based on routine PMTCT testing data for 616 LGAs. The principle finding from this analysis was that there is statistically significant within-state variation in LGA-level HIV prevalence in 62% of Nigerian states. States with higher overall HIV prevalence are more likely to have a wider variation in LGA HIV prevalence than states with lower HIV prevalence at the state level.

Summary of key findings for aim 3

Chapter 4 presented the aim 3 analysis. The third aim was to determine the association between health facility-level factors and maternal and infant HIV outcomes in Malawi's national PMTCT program in 2015-2016. Several facility-level and individual-level factors were found to be significantly associated with infants testing positive for HIV at six weeks postpartum and with mothers being on ART during pregnancy. These associations differed by whether mother-baby pairs sought ANC, PNC, and well child services at the same site consistently (79% of mother-baby pairs), or sought services at multiple sites (21% of mother-baby pairs). Conclusions about facility-level associations for this first group (those receiving all care in the same site) are likely more reliable than

conclusions for the group of mothers who attended multiple sites since facility-level factors may vary considerably between the sites they attended, and this analysis only included measurement of variables for the site the mother attended for well child services. For this reason, results for the stratum of women attending multiple sites for ANC, PNC, and well child services should be interpreted with caution.

For women attending the same site throughout ANC, PNC, and well child care, attending a public health facility was the most significant risk factor for both outcomes. Compared to faith-based facilities, on average, public sector sites had a higher overall patient volume, a higher volume of HIV positive clients, a higher proportion of mothers who attend all ANC, PNC, and well child services at the same site, are more often located in urban areas, and have a lower provider to patient ratio with more doctors but fewer nurses on site. These factors may partially explain this result; however, there may be important unmeasured variables that differ between public and faith-based sites and this should be investigated further. Seeking services at sites with a high provider to patient ratio, a high proportion of pregnant women newly identified as HIV positive, and traveling for more than two hours to reach a site significantly improved the likelihood of mothers being on ART during pregnancy.

The results of this analysis are useful in that they will allow HIV/AIDS program managers in Malawi to prioritize interventions focused on specific facility-level factors shown to be protective against or risk factors for key maternal and infant health outcomes.

However, this analysis is also valuable as an example of how research quality evaluation data can be combined with routine PMTCT program data to facilitate multi-level analyses and expand the scope of questions that can be answered with evaluation data.

Implications of findings and recommendations

This dissertation has important implications both for research, and for public health practice. Below, we offer recommendations for each.

Research implications & recommendations

The aim 1 analysis presented in Chapter 3 raises important questions about the representativeness and validity of ANC-SS-based HIV prevalence estimates in Nigeria. Additional comparisons of ANC-SS data vs routine PMTCT program data should be conducted for other countries, and would help illuminate whether these issues are unique to the Nigerian context, or common in other settings. These analyses would be particularly useful and interesting in countries where there are known discrepancies between the two sources of data, or where the sub-national distribution of the HIV epidemic has been poorly characterized.

The HIV prevalence estimates generated through the aim 2 analysis in Chapter 3 should have high discrimination, given the enormous sample size (n=2.2 million pregnant women tested for HIV) from which they were drawn. Discrimination is critically important for programmatic reasons, allowing public health program managers to

appropriately rank and prioritize sub-national units according to burden of disease, and target interventions accordingly. However, given the known biases in the analytic population (pregnant women, attending ANC, and only those at PEPFAR-supported sites), these HIV prevalence estimates are not well calibrated to the Nigerian population as a whole. Additional research to determine how best to calibrate PMTCT program-data based HIV prevalence estimates to the general population of adults in the absence of regular, reliable large-scale surveillance data would be a major contribution, allowing countries to make use of readily-available program data and further transition away from reliance on surveys and stand-alone ANC-SS for routine HIV/AIDS prevalence estimation.

The aim 3 analysis presented in Chapter 4 had some important limitations that can be addressed with further research. As NEMAPP data collection continues in Malawi, it would be useful to collect additional data on the timing and reason for transfer between facilities among the 21% of women who sought ANC, PNC, and well child services at multiple facilities. Understanding these dynamics would allow us to truly understand the associations between facility-level factors and individual maternal and infant health outcomes for women who received care at multiple facilities.

Public health practice implications & recommendations

Historically, population-based surveys and sentinel surveillance data have been the gold standards for descriptive epidemiologic analyses.[2] However, this reliance on published survey and surveillance data together with legitimate concerns about data quality[3] has

led us to neglect a tremendous resource in routinely collected program data. However, routine program data have evolved over time and data quality has been vastly improved.[4] The World Health Organization now recommends use of PMTCT program data in lieu of ANC sentinel surveillance whenever adequate data quality can be established.[4] Program data has several unique advantages over survey and surveillance data. Given that public health programs are already paying to collect it, program data can be regularly analyzed at no additional cost. The frequency of reporting and regular availability of program data allows public health programs to be nimble and responsive to longitudinal trends over shorter time periods. Issues can be addressed over weeks and months, rather than years. In general, the sample sizes captured through routine program data eclipse those in survey and surveillance data.[4] In Nigeria, for example, program data from one year of PMTCT testing represented a sample size that was 62 times larger than the sample from the latest population-representative survey or last few rounds of ANC-SS.[5–8] Use of program data therefore allows for more granular estimation of disease burden and facilitates diagnosis of programmatic issues at the local level, so that responses can be truly tailored to meet the unique needs of specific populations and sub-populations. Additionally, use of program data for surveillance purposes may motivate data specialists and healthcare workers to improve data quality, and support a culture of data use.[4] And finally, the ethical concerns of unlinked anonymous testing in ANC-SS are alleviated when program data are used as pregnant women are able to opt out of HIV testing if they so choose, and those who consent to be

tested can expect to receive their results and if positive, become aware of their status and offered antiretroviral therapy.[4]

Countries should take advantage of the abundant site-level PMTCT program data now available for their annual UNAIDS HIV prevalence modeling. Spectrum modeling software was updated in 2016 to allow the inclusion of site-level PMTCT program data in addition to ANC-SS and survey data on HIV prevalence,[9] so every effort should be made to ensure all countries have program data of adequate quality for inclusion in these models moving forward. Some basic information (for example, an urban/rural classification for each facility) is required in order for site-level PMTCT program data to be used in the Spectrum model, and updating national site lists with this information should be urgently prioritized. This is particularly critical for countries like Nigeria, and many others in West and Central Africa where the HIV prevalence overall is lower and the distribution of the burden of disease may be poorly understood. In these contexts, the addition of hundreds or thousands of additional data points contributing to HIV prevalence estimates could significantly improve modeled results at sub-national levels.

In addition to the broad implications for use of program data presented above, each of the analyses presented in this dissertation have more immediate implications for public health practice as well. The results of aim 1 indicate that there are important discrepancies between published ANC-SS HIV prevalence estimates and PMTCT program data in Nigeria. Program managers should take note of this and carefully consider how

program data can be used to better inform how resources are prioritized at the state level. The aim 2 analysis showed that most states have significant within-state variation in the burden of HIV, so targeting interventions to whole states is likely not an effective use of limited resources. Instead, LGAs should be ranked and prioritized based on burden of HIV, with programmatic responses tailored to the epidemic in each LGA. This will reduce waste and ensure that resources are invested where they are most urgently needed to change the course of the HIV/AIDS epidemic in Nigeria. Finally, the aim 3 results should be used to focus interventions on facility-level factors shown to produce negative maternal and infant health outcomes in Malawi. Specifically, additional analysis of why PMTCT programs at faith-based facilities are producing better maternal and infant outcomes than public sector sites should be supported. Strategically distributing nurses and doctors across public sector facilities to maximize the average provider to patient ratio should be a priority,[10] and in some cases, it may be necessary to hire additional nurses and doctors to achieve an adequate provider to patient ratio. Sites with a high proportion of pregnant women newly diagnosed with HIV may require additional resources in the form of counselors, peer mothers, or linkage facilitators[11] in order to ensure that newly diagnosed mothers have the information and support they need to not only successfully initiate ART, but to adhere to it throughout pregnancy and breastfeeding.

Continually working to improve the reliability of PMTCT program data will further enhance its usability for these sorts of analyses. Improving the quality of routine public

health program data should be a shared priority for all public health program managers. The ability to regularly estimate local prevalence and disease burden using routine programmatic data can vastly improve the ability of public health program managers to track epidemics at sub-national levels on a continuous basis. Additionally, having reliable site-level programmatic results available on a monthly or quarterly basis allows public health program managers to keep their finger on the pulse of their programs, and to be nimble in addressing problems as they arise. The real time use of granular program data has tremendous promise for improving the cost effectiveness, efficiency, and lifesaving potential of public health programs.

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Appendix: NEMAPP protocol

EVALUATING THE EFFECTIVENESS AND IMPACT OF THE PREVENTION OF MOTHER TO CHILD TRANSMISSION OF HIV PROGRAM IN MALAWI: A NATIONAL STRATEGY OF "TEST AND TREAT" FOR ALL PREGNANT AND BREASTFEEDING WOMEN

NATIONAL EVALUATION OF THE MALAWI PMTCT PROGRAM (NEMAPP)

MINISTRY OF HEALTH, MALAWI

IN COLLABORATION WITH THE CENTERS FOR DISEASE CONTROL AND PREVENTION

ACKNOWLEDGEMENTS: *The South African PMTCT Effectiveness Survey at MRC with special thanks to Drs. Ameena Goga, Debra Jackson and Thu-Ha Dinh for sharing the South Africa and Zimbabwe survey protocols with the Malawi MOH PMTCT Effectiveness Steering Committee.*

Executive Summary

Background

In 2010 WHO issued new recommendations on Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV infection in Infants, Antiretroviral Therapy for HIV Infection in Adults and Adolescents, and Antiretroviral Therapy for HIV Infection in Infants and Children, based on current research evidence. Some key aspects of these recommendations include (but are not limited to); earlier initiation of antiretroviral therapy (ART) to slow disease progression, increase survival and reduce HIV transmission; phasing out of Stavudine (d4T) regimens to reduce long term side-effects; use of more efficacious regimens for the prevention of mother to child HIV transmission (PMTCT), starting at 14 weeks gestation and continuing through labor and breastfeeding to further reduce vertical transmission and improve maternal and child health outcomes.

In response to these recommendations, the Ministry of Health (MOH) Department for HIV and AIDS led the technical working groups (TWGs) for PMTCT and ART in writing the 1st Edition of the Malawi Guidelines for the Clinical Management of HIV in Children and Adults. This document defines the framework for Malawi's national HIV programs and fully integrates programs for PMTCT, follow-up of HIV-exposed infants, pre-ART follow-up for children and adults, ART and family planning (FP). The MOH of Malawi endorsed Malawi's Revised Policy for PMTCT and ART.

Implementation of the new integrated PMTCT/ART guidelines began in July 2011, with HIV-infected pregnant and breastfeeding women starting lifelong ART, regardless of CD4 or clinical stage. Infants born to HIV-infected women receive 6 weeks of nevirapine (NVP). HIV-infected infants under the age of 2 years will initiate lifelong ART regardless of CD4 measurement. There is provider-initiated provision of Family Planning (Depo-Provera and condoms) in pre-ART and ART clinics and wherever possible, ART is now provided in ANC.

The MoH wishes to evaluate the effectiveness of the new integrated approach to PMTCT in Malawi through this proposed study which will serve as a basic program evaluation.

A separate protocol will be written to evaluate the qualitative aspects of the current program including determinants and processes of decision-making around uptake, retention, and adherence of mother and child in integrated PMTCT/ART program; the perceived and experienced institutional/ behavioral/ community barriers to uptake, retention and adherence in PMTCT; and identification of community networks which are perceived to strengthen father, mother and child uptake of and retention in HIV services.

Objectives of the study

There are three primary and seven secondary objectives in the study, which will be answered at the zonal or sub-national level.

Primary Objectives:

i. Measure mother-to-child HIV transmission rates in an age-based (4-26 weeks) cohort of HIV-exposed infants at 4-12 weeks, 12 months and 24 months post-partum, and compare rates over time

ii. Measure HIV-free survival in an age-based (4-26 weeks) cohort of HIV-exposed infants at 6-12 weeks, 12 months and 24 months of age, and compare rates over time

iii. Measure longer term survival and virological and clinical outcomes in a sub-set of mother-child pairs who will receive extended follow up to 48 months post-partum, after they initiated ART under option B+.

Secondary Objectives

i. Measure rates of ARV initiation, retention, and adherence amongst a cohort of HIV-infected mothers and their infants enrolled within the integrated PMTCT/ART program

ii. Compare outcomes of age-based cohorts of infants, and their mothers, included mortality, loss-to-follow-up, and ART coverage in ANC.

iii. Estimate any association between mother-infant pair outcomes and ARV regimen, maternal background characteristics including CD4 cell count, maternal health care services and maternal and infant health status

iv. Measure viral suppression up to 48 months in a cohort of HIV positive mothers who started (and continued) ART as part of the Option B+ program

v. Describe associations of virological, immunological and clinical outcomes (including toxicities) with maternal and infant characteristics among a subgroup of mother-child pairs followed up to 48 months.

vi. Validate HIV rapid testing at study sites in women who have received previous positive and negative results using ELISA testing

vii. Validate HIV rapid testing at study sites and compare sensitivity of rapid testing against ELISA testing and DNA PCR testing at detecting HIV infection among infants aged 12 months

Overview of Methods

This study will follow up to three cohorts each of 3,376 HIV-exposed 4-26 week old infants and their mothers until 24 months of age or weaning. Infants will be identified at a visit to an under 5 clinic. These cohorts will undergo HIV testing at enrollment, 12 months and at 24 months of age. Trained study staff will conduct a brief interview with

mothers and caregivers at a private location in the clinic at each study visit. Mother-infant pair data will be abstracted on a quarterly basis from standard national data tools held at the study sites and analyzed to describe outcomes. HIV exposure status in infants will be determined by ELISA testing of both mothers and infants. For those infants unaccompanied by their mothers, infant HIV exposure status will be determined by rapid test with ELISA confirmatory testing.

For the child's 12 and 24 month follow-up visits, HIV rapid testing will be conducted at the site, followed by confirmatory ELISA and PCR testing. Outcomes will be described at 6-12 weeks of age, 12 and 24 months of age. A subset of 1,324 mother-infant pairs will receive annual study visits up to 48 month post-partum to determine survival, standardized ART outcomes, and undergo maternal blood sampling for HIV-1 RNA, CD4 count and when indicated, hepatitis B serology. In a smaller subset of 500 mother-infant pairs (out of the 1,324), enhanced follow up for more detailed description of morbidity, growth, adverse effects and drug toxicity, recurrent pregnancies and family planning utilization will be done through quarterly study visits.
Consent forms administered during this study will ask for consent for storage, and testing of leftover DBS in other studies which are anticipated to use data and samples collected from this cohort of mother-infant pairs, including evaluation of resistance among HIV-infected infants and their mothers. In the event somebody wishes to withdraw themselves and their samples from the study, the samples will be destroyed in accordance with national laboratory guidelines.

A separate but linked protocol will be submitted for approval during the first year of the study to assess ANC and PMTCT-related decision-making processes in women, male partners and community members.

The Malawi Ministry of Health will fund and oversee this study in collaboration with the Centers for Disease Control and Prevention (Malawi Office), and with implementation support from partners in-country.

Outcome
It is anticipated that findings from this study will describe the impact and effectiveness of the Malawi option B+ PMTCT program and guide program managers at national and zonal levels in future decision making. The results will be used to describe progress towards achieving the goals of the National Action Framework, National HIV/AIDS Strategic Plan and Elimination of Mother-to-Child Transmission (EMTCT) Strategy.

Future evaluations
The Ministry of Health may wish to repeat this activity in the future, in which case an amendment to this protocol will be submitted to the CDC Center for Global Health Associate Director of Science, and the Malawi Ministry of Health National Health Science and Research Committee (FWA: IRB00003905).

Investigators, Advisors and Collaborators and Roles

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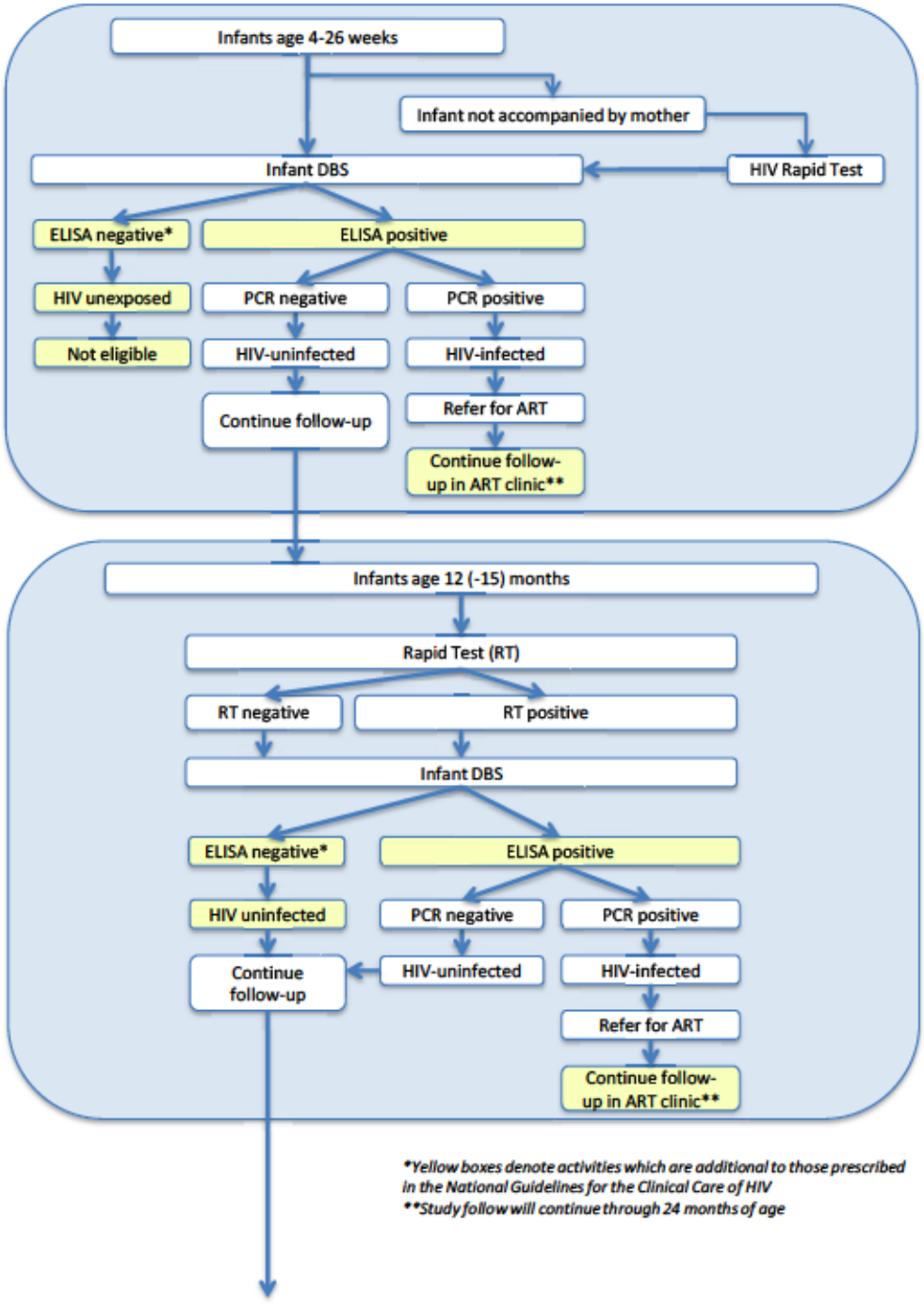
Roles of Investigators, Advisors and Collaborators

	Study Funding	Member Steering Committee	Protocol Development	SOP Development	Training	Study Implementation	Logistics	Laboratory	Study Monitoring	Data Management	Data Analysis	Updates to National TWG	Dissemination of Results	Knowledge Translation
Dr. Frank Chimbwandira		X										X	X	X
Dr. Beth Tippett Barr	X	X	X						X		X	X	X	X
Mr. Blackson Matatiyo	X	X											X	X
Dr. Andreas Jahn		X	X						X	X	X		X	X
Mr. Michael Eliya		X							X				X	X
Dr. Erik Schouten		X	X	X	X	X	X	X	X	X	X	X	X	X
Dr. Scott Kellerman			X	X							X		X	
Dr. Monique van Lettow		X	X	X	X	X			X	X	X	X	X	X
Prof. Joep van Oosterhout		X	X	X		X			X				X	X
Dr. Megan Landes			X	X					X		X		X	
Mrs. Dalitso Midiani		X							X				X	X
Dr. Sundeep Gupta			X								X		X	
Dr. Nellie Wadonda-Kabondo,		X	X						X		X		X	
Dr. Alice Maida, CDC Malawi									X				X	
Dr. Thu-Ha Dinh			X								X		X	X
Dr. Helen Dale			X								X		X	X
Ms. Jennifer Sabatier										X	X		X	
Dr. Elliot Raizes			X										X	
Dr. Josef Amann			X										X	
Dr. Abdoulaye Sarr				X			X	X					X	
Dr Fabian Cataldo			X			X							X	X
Mr Ruben Mwenda				X				X					X	X
Dr Catherine Mundi				X				X						
Mr Jean Bourgeois				X						X				
Malawi Ministry of Health HIV Technical Working Group and PMTCT/ART group														X
Government of Malawi Office of the President and Cabinet (OPC)														X

NEMAPP Tables and Figures



Yellow boxes denote activities which are additional to those prescribed in the National Guidelines for the Clinical Care of HIV

***Study follow will continue through 24 months of age*

EVALUATING THE EFFECTIVENESS AND IMPACT OF THE PMTCT PROGRAM IN MALAWI: A NATIONAL STRATEGY OF "TEST AND TREAT" FOR ALL PREGNANT AND BREASTFEEDING WOMEN

1.Introduction

In this protocol, our primary objectives are to evaluate the impact of the national integrated PMTCT/ART program in Malawi on rates of mother to child transmission (MTCT) of HIV, HIV-free survival of HIV-exposed infants and young children, and viral suppression in women initiated on ART under Option B+. This activity, which will be conducted in ten districts from all health administrative zones of Malawi, will prospectively follow a cohort of mother-infant pairs[1] (with infant aged 4-26 weeks at enrolment) to describe maternal and infant outcomes.

1.1 Literature Review

Malawi has a population of 15.3 million, with a generalized HIV epidemic which has led to an estimated adult national HIV prevalence of 11% in 2009 and 920,000 people living with HIV/AIDS, of which 120,000 are children aged 14 years or less (1). There are 608,000 births annually, and in 2010 the national HIV prevalence among pregnant women was estimated to be 11.8% (2) The total fertility rate in Malawi is high at 5.7 births per woman (3), meaning that after a median breastfeeding duration of 23 months (4) the majority of women become pregnant again. It is estimated that about 20,000 children become infected every year through mother to child transmission of HIV virus but this is projected to decline rapidly with the implementation of PMTCT Option B+ (HIV surveillance report 2010).

Without any intervention, and in a breastfeeding population, 20-45% of infants born to HIV-infected mothers will acquire the infection during pregnancy, labor and delivery, and breastfeeding (5). The use of antiretroviral drugs (ARVs) has been shown to reduce the risk of mother-to-child HIV transmission (MTCT). Early interventions in resource-constrained settings relied on single dose nevirapine (sdNVP) which significantly reduced peripartum MTCT rates, was easy to administer and cost-effective. However, this strategy provided no protection to the infant during breastfeeding and research showed that it led to development of viral resistance in mother and infant (6). The World Health Organization (WHO) issued guidelines in 2006 for the use of ARVs to treat pregnant women and prevent infection in infants (7) which moved beyond the use of sdNVP by recommending a combination of ARVs for more effective prophylaxis during the last trimester (from 28 weeks gestation) and early post-partum period. However, under these guidelines the infant was unprotected from HIV acquisition during the

[1] The term "Mother-Infant Pair" is inclusive of any woman who is not the biological mother of an HIV-exposed child, but who has an HIV-exposed child in their care and who will be followed with the child for the duration of the study.

breastfeeding period, and antiretroviral therapy for ongoing treatment (ART) was only recommended for pregnant and breastfeeding women who met eligibility criteria.

Subsequently, observational data suggested that starting ARV prophylaxis earlier in pregnancy may be more effective in reducing MTCT (8, 9). More rigorous evidence then emerged on: The use of ARVs to prevent MTCT (10), including during breastfeeding (11, 12, 13, 14); optimal times for initiation of ART among people in need of it for their own health; and safer infant feeding practices. In response, in 2010 WHO issued new recommendations on the use of 'Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants' (15); these were preceded by a rapid advice document issued in 2009 (16). WHO recommended two ARV prophylaxis regimens, Option A and Option B, both of which are heavily dependent on a strong lab system capable of providing CD4 count for initiating and stopping ART (17):

Table 1. Option A and Option B WHO recommendations

Option A: Maternal AZT	**Option B: Maternal triple ARV prophylaxis**
MOTHER Antepartum AZT from 14 weeks onwards sdNVP at onset of labor AZT+3TC during labor and delivery* AZT+3TC for 7 days post-partum*	**MOTHER** Triple ARV from 14 weeks until 1 week after exposure to breast milk has ended AZT+3TC+LPV/r AZT+3TC+ABC AZT+3TC+EFV TDF+3TC (or FTC) +EFV
INFANT <u>Breastfeeding infant</u> Sd-NVP at birth plus daily NVP from birth until 1 week after exposure to breast milk has ended <u>Non-breastfeeding infant</u> Sd-NVP at birth plus AZT or NVP from birth until 4-6 weeks	**INFANT** <u>Breastfeeding infant</u> AZT or NVP until 4-6 weeks <u>Non-breastfeeding infant</u> AZT or NVP from birth until 4-6 weeks

*sd-NVP and AZT+3TC can be omitted if mother receives >4 weeks AZT antepartum

In April 2012, WHO issued a programmatic update on the "Use of Antiretrovirals for Treating Pregnant Women and Preventing HIV Infection in Infants" (18). This update was issued to provide countries with additional information since WHO issued the PMTCT ARV guidelines in 2010, and was particularly important as other countries were starting to follow the Malawi example and were preparing to implement Option B+.

Viral Load monitoring for patients on ART is the standard of care in well-resourced settings such as Europe and the United States (20, 21). Viral load suppression in patients on ART suggests high levels of adherence (22) and predicts favorable treatment outcomes (23).

1.2 Malawi PMTCT Program

The PMTCT program started in Malawi in 2004, and despite several years of slow growth, has made significant progress since 2009. In early 2007 only 140 sites provided PMTCT services, and by March 2011 486 antenatal clinics were providing PMTCT services (23). Approximately 97% of pregnant women attend ANC at least once, 72% of deliveries are at a health facility and 72% of infants under 6 months of age are exclusively breastfed (3).

In response to the 2010 WHO recommendations, Malawi revised the national policies for PMTCT and for ART to reflect a public health approach based on WHO recommendations, while taking into account the country context and ensuring that ART access for pregnant women was not solely dependent on CD4 capacity at facilities. Access to CD4 cell count analysis in Malawi is minimal and health system barriers are not likely to change quickly (24, 25). Specifically, the minimal access to CD4 counts despite efforts to strengthen lab services meant that dependence on this test would adversely affect scale-up of PMTCT and early ART initiation. The new guidelines were intended to rapidly increase coverage of PMTCT and ART and reduce transmission (vertical and horizontal) without being handicapped by known health system weaknesses.

Malawi has taken a unique approach, now coined "Option B+", where all HIV-infected pregnant or breastfeeding women are offered lifelong ART (Tenofovir, Lamivudine and Efavirenz), in the form of a single pill taken once a day. Currently, no other country has taken this approach in their revision of national PMTCT guidelines. Malawi Ministry of Health used a strong evidence base to argue that Option B+ offers the following advantages:

1. It is simple to implement
2. Will reduce maternal post-partum mortality
3. Prevents exposure to single ARV prophylaxis in women with advanced HIV disease
4. Facilitates equitable access to PMTCT and ART
5. Virtually eliminates pediatric HIV/AIDS
6. Reduces HIV transmission risk for uninfected male partners
7. Provides protection for the next pregnancy
8. Decreases risk of tuberculosis
9. Reduces HIV/AIDS mortality
10. Treats hepatitis B co-infection

Studies and mathematical models have shown that implementation of a 'test and treat' approach and early initiation of ART can reduce HIV incidence and mortality to less than 1 case per 1,000 people per year within 10 years (26, 27). Option B+, which is based on

this understanding, was launched in July 2011, and it is estimated that in the first 3 years of implementation over 25,000 pregnant or breastfeeding women will start ART each year. PMTCT/ART providers are predominantly nurses, clinical officers and medical assistants, and were trained in a 5-day intensive integrated ART/PMTCT curriculum. Over a six month period, almost 90% of all service providers in Malawi were trained to use the new guidelines.

Quarterly ANC program data from March 2012 show that 76% of ANC attendees had their HIV status ascertained and 7% were HIV-positive. However, comparison of ANC Surveillance data, ANC program data and the DHS 2010 show significant discrepancies in HIV prevalence amongst pregnant women, leading to questions around the sensitivity of the HIV testing conducted in ANC. CDC provided technical assistance for a national HTC review, which highlighted significant protocol drift in all HTC settings. Malawi is currently revising the HIV testing algorithm and evaluating a change in the test kits used nationally. Validation of HTC in ANC settings is incorporated into this protocol. Seventy-six percent of HIV-infected women attending ANC received any maternal ARVs (for prophylaxis or treatment), which represent 46% coverage of the estimated HIV-infected pregnant women in the population in Quarter 2, 2011. Of those ANC attendees receiving any ARVs, 8% received sd-NVP to take home, 23% initiated AZT combination regimen and 12% of HIV-infected ANC attendees received infant doses of ARVs (sd-NVP syrup) to take home (28).

Current retention rates within the national ART program are relatively high. Of the 477,022 patients ever initiated on ART, 347,983 (73%) were retained alive on ART by the end of the first quarter of 2013 (28). Twelve month adult ART cohort retention rates are currently 80% in the first quarter data of 2012. However, this data is based mainly on patients who initiated ART for their own health. It is unclear what adherence and retention rates will be among pregnant and breastfeeding women who initiate ART while still in good health.

Timing well with the transition of the national PMTCT program, Malawi was the recipient of $10 million additional PMTCT funding under PEPFAR for FY10 and FY11, provided to six countries and requiring a scale-up plan to reach universal access to PMTCT for pregnant women. Conditional to the funding was the earmarking of 10% for program evaluation, funding which will be utilized with the implementation of this protocol. Additional funding has been earmarked each fiscal year since, and is anticipated to continue through the duration of the study. Best practices and lessons learned will be identified and shared at all levels in order to inform the national program. In this protocol, we aim to evaluate the impact of PMTCT Option B+ on the rates of MTCT of HIV.

1.3 Study Justification

Simple modeling on existing and anticipated improvements in PMTCT coverage and regimen shows that loss-to-follow-up across the PMTCT cascade significantly impacts

final transmission rates at both program and population level. However, no system exists which monitors MTCT and tracks the linkage and progress of the mother-infant pair through the continuum of care. Recently a cross-sectional survey was conducted in Malawi by Management Sciences for Health (MSH) in collaboration with the MOH to evaluate MTCT of HIV in HIV-exposed infants under 3 months of age. This evaluation will build on the MSH experience and the South African PMTCT Evaluation Protocol to provide comprehensive information about the effectiveness of Malawi's National PMTCT program throughout the duration of the infant exposure period.

Given the massive uptake of ART in the implementation of Option B+ in Malawi, it is also important to assess broader maternal outcomes including retention, adherence, adverse events, and HIV-related complications such as tuberculosis (TB), other opportunistic infections (OIs) and mortality.

1.4 Intended use of findings

This is the first nationally representative study on impact of the Malawi PMTCT program. The findings will be used primarily to inform the management of Malawi's integrated ART/PMTCT program. In addition, the study will provide critical insight into the impact and effectiveness of a test and treat approach at population level. The study findings will be disseminated to all stakeholders including the relevant national technical working groups (TWGs), the National AIDS Commission (NAC), the Office of the President and Cabinet (OPC), UNAIDS, UNICEF, WHO, and key implementing partners in country. Findings will also be disseminated at international meetings and in peer-reviewed journals to ensure other national programs and global policy makers are reached. All presentations and publications will include author representation from each of the institutions involved in the study, following internationally accepted authorship guidelines.

1.5 Objectives

There are three primary and seven secondary objectives in the study, which will be answered at the zonal or sub-national level.

1.5.1 Primary Objectives

i. Measure rates of mother-to-child HIV transmission postpartum at 6-12 weeks, 12 months and 24 months, and compare over time

ii. Measure HIV-free survival at 12 and 24 months of age, and compare over time

iii. Measure longer term survival and virological and clinical outcomes in a sub-set of mother-child pairs who will receive extended follow up to 48 months port-partum, after they initiated ART under option B+.

1.5.2 Secondary Objectives

i. Compare rates of ARV initiation, retention, and adherence amongst a cohort of HIV-infected mothers and their infants enrolled within the integrated PMTCT/ART program

ii. Compare outcomes of age-based cohorts of infants, and their mothers, included mortality, loss-to-follow-up, and ART coverage in ANC.

iii. Estimate any association between mother-infant pair outcomes and ARV regimen, maternal background characteristics including CD4 cell count, maternal health care services and maternal and infant health status

iv. Measure viral suppression up to 48 months in a cohort of HIV positive mothers who started (and continued) ART as part of the Option B+ program

v. Describe associations of virological, immunological and clinical outcomes (including toxicities) with maternal and infant characteristics among a subgroup of mother-child pairs followed up to 48 months

vi. Validate HIV rapid testing at study sites in women who have received previous positive and negative results using ELISA testing

vii. Validate HIV rapid testing at study sites and compare sensitivity of rapid testing against ELISA testing and DNA PCR testing at detecting HIV infection among infants aged 12 months

1.6 Study Implementation and Oversight

This study will be implemented by Management Sciences for Health (MSH) in collaboration with Dignitas International (DI). MSH will take overall responsibility for all study details including preparation of SOPs, data records and management, all study monitoring and compliance reviews.

Oversight for this evaluation will be managed by a steering committee co-chaired by the PI's, MOH and CDC-Malawi. The members of the steering committee include the investigators and technical advisors. The steering committee will be responsible for the overall quality of the study, and adverse event reporting to the IRBs. All final results will be bound in a report and submitted to the MOH, PEPFAR and the national TWG.

1.7 General approach

The evaluation will have three components: a) HIV-exposure screening of approximately 37,000 (until the number to be followed up is reached) 4-26 week old infants and their mothers who are attending under-5 clinic, b) prospective follow-up of all confirmed HIV-exposed and infected infants through 24 months of age, with the following defined outcomes: Death, loss-to-follow-up (LTFU) before 24 months, confirmed HIV-infection (and subsequent initiation on ART), or confirmed HIV-free survival at the end of the breastfeeding period (approximately 24 months of age), and c) prospective follow up of a sub-set of mother-infant pairs to determine long-term

survival and monitor virological, immunological and clinical outcomes up to 48 months port-partum.

Infants will be identified at selected sites when they are attending an under-5 clinic. This cohort will undergo HIV testing at the time of initial enrollment, at 12 months and 24 months of age. Infants breastfeeding beyond 24 months of age will receive a final diagnosis after weaning.

All consenting mothers will receive a brief interview at the time of enrollment and at infant 12 and 24-month testing points. Mother-infant pair outcomes will be measured using individual medical record data abstracted from the MOH maternal and infant ART cards, and the Exposed Child Under 24 Months Card, as well as interview data and data confirmed where possible from patient-held health passports during interview. A subset of mother-infant pairs will be selected for extended and enhanced 48 month follow-up, monitoring virologic, immunological and clinical outcomes On a quarterly basis data will be abstracted from the infant and mother records, until final HIV infection and survival status at age 24 months is determined and/or until the study ends. All HIV-infected mothers and their children will be referred to routine HIV care and treatment services, as per national guidelines. All mothers will be screened for prior HIV test results and ART status, and all mothers regardless of previous or current test results will have ELISA-testing of DBS conducted to validate those results[2]. Consenting mothers who started ART during or after the most recent pregnancy and were selected for extended follow-up will undergo sampling for HIV-1 RNA, CD4 count and hepatitis B serology at enrolment (approximately 6 months post ART initiation), and at 12, 24, 36 and 48 months post ART initiation, and an additional short interview at maternal testing points.

In a subset of 500 mother-infant pairs, enhanced follow up for more detailed description of morbidity, growth and development, adverse effects and toxicities, recurrent pregnancies and family planning utilization will be done through quarterly study visits. (Appendix 3 gives a more detailed description of the extended 48 month cohort)

To determine HIV exposure status of infants aged 4-26 weeks, in addition to the routinely recommended screening of the maternal health passport for HIV test results, ELISA testing on infant Dry Blood Spots (DBS) will be conducted at a central laboratory, followed by DNA-PCR for those who are ELISA-positive. For infants whose mothers have died, rapid testing will be done (as per MOH guidelines) followed by ELISA testing for validation of the rapid testing and PCR for confirmation of positive ELISA results.

For infants 12 month follow-up visit, HIV rapid testing will be conducted at the site (as per MOH guidelines), followed by confirmatory ELISA testing at the central lab. All

[2] This ELISA confirmation is at MOH request, as validation of rapid HIV testing in high-burden ANC settings is warranted given a recent CDC-conducted evaluation of the national HTC program.

samples with positive ELISA results will undergo PCR testing in order to compare the sensitivity of HIV rapid test results with DNA PCR results at detecting HIV infection in infants aged 12 months, thus validating the MOH current national guidelines for HIV testing of 12 month olds. For infant 24 month follow-up visits, HIV rapid testing will be conducted at the site, with confirmation of results by ELISA testing. If a child is still breastfeeding at 24 months, they will be retained in the study until 6 weeks after weaning and a final diagnosis is given.

For patients who are more than two weeks late for a study visit, active tracing by community follow-up will be utilized.

An additional complementary qualitative protocol will be submitted in the first year of the study to increase understanding of individual and family decision-making behind uptake and retention in PMTCT and ART, challenges experienced by both service providers and recipients, provide insight into the transmission rate observed in infants and young children, and provide guidance on improving program implementation at facility and community levels. It will also take into account provider: patient ratios, provider qualifications and years of service, and provider workload.

1.7.1 Rapid Site Assessment

A rapid site assessment will be conducted to determine the availability and capacity for rapid HIV testing and counseling (HTC), DBS for ELISA and PCR in under-5 clinics, and availability of and access to HIV care and treatment services for HIV-exposed and infected infants and children and their mothers. Once this has been done (planned to take place in the first 3 months of the study), MOH staff will strengthen services and develop linkages to ensure that mothers are offered rapid HIV testing according to the national guidelines; samples are collected from all HIV-exposed infants to undergo HIV testing according to national guidelines; HIV-infected mothers and infants will receive quality HIV care and treatment services in a timely manner; and DNA PCR test results are returned to the sites in a timely manner. In this way, the study will contribute to system strengthening and capacity building.

1.7.2 Study pilot

All study activities described in this protocol will be piloted at a small sample of non-study sites. Approximately 5-10 participants will be administered the questionnaires as part of the pilot; the primary objective will be to test flow of questions and basic understanding by the participants. Adjustments to tool and/or data entry platform will be made after the pilot as necessary. If there are any significant changes needed from the original protocol/questionnaire, the PIs will be responsible to report to Malawi and CDC ethics committees. Based on the overall findings of the pilot, investigators may submit a protocol amendment revising any methodologies to ensure study objectives are met.

2. Procedures/Methods

2.1 Design

A cohort of HIV-exposed infants aged 4-26 weeks will be enrolled into the study. National coverage of the 1st immunization (DTP) is 95% (17), although many infants present later than the recommended age, with less than 70% receiving their first vaccination before 12 weeks of age and approximately 95% by 26 weeks (18). By enrolling HIV-exposed infants aged 4-26 weeks who are attending an under-5 clinic, investigators believe the study cohort will be reasonably representative of all HIV-exposed infants in Malawi, and will identify mother-infant pairs previously lost-to-follow-up in ANC and/or ART during pregnancy.

A baseline determination of infant HIV exposure status and infection status at the time of enrollment will be made using ELISA testing and DNA PCR testing respectively on DBS. Early transmission rates will be estimated in only those infants who are aged 4-12 weeks at enrolment.

All infants will be prospectively followed up and tested to determine transmission rates at 12 and 24 months, and a subset of mother-infant pairs will be followed up through 48 months. Follow-up will be conducted at the same facility where the infants receive routine MOH Under-5 and HIV Exposed-Infant care until 24 months of age or weaning. Quarterly data abstraction from infant and maternal medical charts will be used to determine outcomes of interest including rates of ARV initiation, retention, and adherence among HIV-infected mothers and their infants, compare outcomes of age-based cohorts, and determine any association between mother-infant pair outcomes and ARV regimen, maternal background characteristics including CD4 cell count, maternal health care services and maternal and infant health status.

In summary, from the baseline enrolment survey, a cohort of HIV-exposed infants aged 4-26 weeks will be identified and followed until 24 months postpartum.
The baseline enrollment survey will provide:

I. HIV prevalence amongst HIV-exposed infants presenting for their first vaccination visit (regardless of age)
II. An estimate of early vertical transmission among infants aged 4-12 weeks
III. Identify representative HIV-exposed but uninfected infants to be enrolled into the prospective cohort

The main study cohort follow-up will provide estimates of:

I. HIV prevalence among infants aged 12 months and 24 months
II. HIV-free survival among infants aged 12 months and 24 months.
III. Coverage of PMTCT program indicators in the post-partum period through 24 months

The 48-month follow-up of a subset of mother-infant pairs will provide estimates of:

I. Long term survival and retention in ART for women who were initiated on ART under Option B+

II. Viral suppression and genotypic resistance in those with detectable HIV-1 RNA

III. Clinical and immunological outcomes of mother-child pairs including health status, morbidity, toxicity and mortality.

Investigators will also review national aggregate data to describe overall program outcomes.

Audience and stakeholder participation

The Ministry of Health will present the protocol to the PMTCT/ART technical working group. These stakeholders will be regularly updated semi-annually on of the progress of the study. At the end of the study, all results will be bound in a report.

2.2 Study population

2.2.1 Source

The study population consists of HIV-exposed infants attending an under-five clinic, and their mothers/caregivers. Exposure to HIV infection will be determined by baseline HIV testing.

Caregivers of infants whose mothers have died will also be tested for HIV. It is likely that the caregiver who brings a child to under-5 clinic is the full-time provider of that child, and may also be breastfeeding the child. HIV testing is routine clinical care in Malawi, and as HIV-exposed infants are not excluded from the study if their mothers have died, the HIV status of the caregiver is also needed for the study.

2.2.2 Criteria for screening for enrolment into study

Inclusion Criteria

- Infants aged 4-26 weeks and their mother or caregiver
- Mother/caregiver willing and able to consent

Exclusion Criteria

- Children aged 27 weeks and above
- Infants aged less than 4 weeks
- Infants whose mother is alive but not present; except if the father is the caregiver presenting with the child (if alive, only a parent can consent for the study)

2.2.3 Case Definitions

For the purposes of this study[3], the following definitions are used:

An **HIV-exposed infant** is defined as:

a) An infant with a documented ELISA positive HIV test result, **OR** an infant of a mother with a newly documented positive ELISA HIV test result received during the study

b) Any infant of an HIV-positive mother (confirmed ELISA test positive) who is breastfeeding

An **HIV-exposed child** is defined as:

a) Any child 12 months or older who was enrolled in the study during infancy, and who doesn't have a final diagnosis

b) Any child of an HIV-positive mother (confirmed ELISA test positive) who is breastfeeding

An **HIV-infected infant** is defined as:

a) An infant with a documented positive HIV DNA PCR test result performed at age 6 months or less

An **HIV-infected child** is defined as:

a) For 12 month transmission: A child between 12 and 15 months who received a documented positive HIV DNA PCR test result

b) For 24 month or final transmission: A child aged 24 months or above with a documented positive ELISA test result OR a positive HIV DNA PCR test result

An **HIV-uninfected infant** is defined as:

a) An infant who receives a negative DNA PCR test

An **HIV-uninfected child** is defined as:

a) For 12 month transmission: A child between 12 and 15 months who received a documented negative HIV DNA PCR test result

b) For 24 month or final transmission: A child aged 24 months or above with a documented negative ELISA test result OR a negative HIV DNA PCR test result

A **final HIV status** of HIV-uninfected would apply if last exposure to breast milk was at least 6 weeks prior to receiving either of the test results listed above.

A **mother** is the biological mother of the infant.

[3] Please note these definitions are specific to this study and not the same as the National HIV Guidelines; all testing will follow the study protocol in addition to the national guidelines testing algorithm.

A **mother-infant pair** is the paired adult and child followed for the duration of the study. The term is inclusive of any adult who is the non-biological parent of an HIV-exposed infant and who presents as the caregiver of the HIV-exposed infant.

A **caregiver** is any person other than the biological mother who presents with an infant or child at an under-5 clinic.

2.3 Sampling

The primary sampling objective is the drawing of a nationally representative sample of participants across Malawi to provide national as well as sub-national estimates of MTCT. The primary sampling unit is the health facility, and the sampling frame includes all 579 health facilities which provided PMTCT services in Malawi in 2012. This national evaluation uses a stratified multistage cluster sampling design to identify and enroll cohorts of mother infant pairs.

Sampling frame

Due to homogeneity within the Ministry of Health Administrative Zones, four zones were utilized as the baseline strata for the study; based on epidemiologic and programmatic similarity, North, Central West and Central East Zones were combined (referred to as North-Central) and Lilongwe District is kept as a separate stratum. In addition, South West and South East Zones were merged (referred to as 'South'), and Blantyre District is kept as a separate stratum due to variation from the other districts in the Southern zones. This level of analysis will still be referred to as "Zonal" level.

Stage 1: Site Sampling

A total of 66 sites were determined to be needed for all strata: this was calculated starting with 25 sites per stratum (and estimated maximum feasible number to manage), and then applying the finite population correction factor (FPC) calculation to each stratum. The sample size per strata was then divided by the number of sites in that strata, resulting in 52 enrollees for each site selected. Sites were then sorted using a proxy measure for performance, created using available data, by multiplying the proportion of women tested for HIV in ANC by the proportion of positive women who started ART, and again by the proportion of women who were retained in Option B+ at 6 months. Probability-proportional-to-size (PPS) selection without replacement was then used to select the sites for the evaluation. As some large sites were selected more than once, the final number of sites is 55: 14 in North/Central, 10 in Lilongwe, 22 in South, and 9 in Blantyre.

Stage 2: Patient Sampling

We will consecutively enroll patients for logistical and feasibility reasons. While not enrolling in a random or systematic fashion could introduce some bias, we feel that it will be minimal, and different sites will have enrollment during or throughout different parts of the 12 month period until they reach the required sample size. For details on enrolment of mother-pair subsets, please see Appendix 3.

2.4 Sample size estimate

Selected study sites are listed in Appendix 1, and sample size calculations are described in detail in Appendix 2.

Using national DHS, HIV Program and ANC Surveillance data for ANC registrations, HIV prevalence in ANC, HIV testing, ART before and during pregnancy, and retention in care, the number of HIV-exposed deliveries was estimated. We then used the known MTCT rates for 4-12 weeks, 12 months and 24 months for different PMTCT prophylaxis regimens, and using the proportion of HIV-infected women on these different regimens nationally and by zone, we calculated estimated *population-based* MTCT rates for 4-12 weeks, 12 months and 24 months.

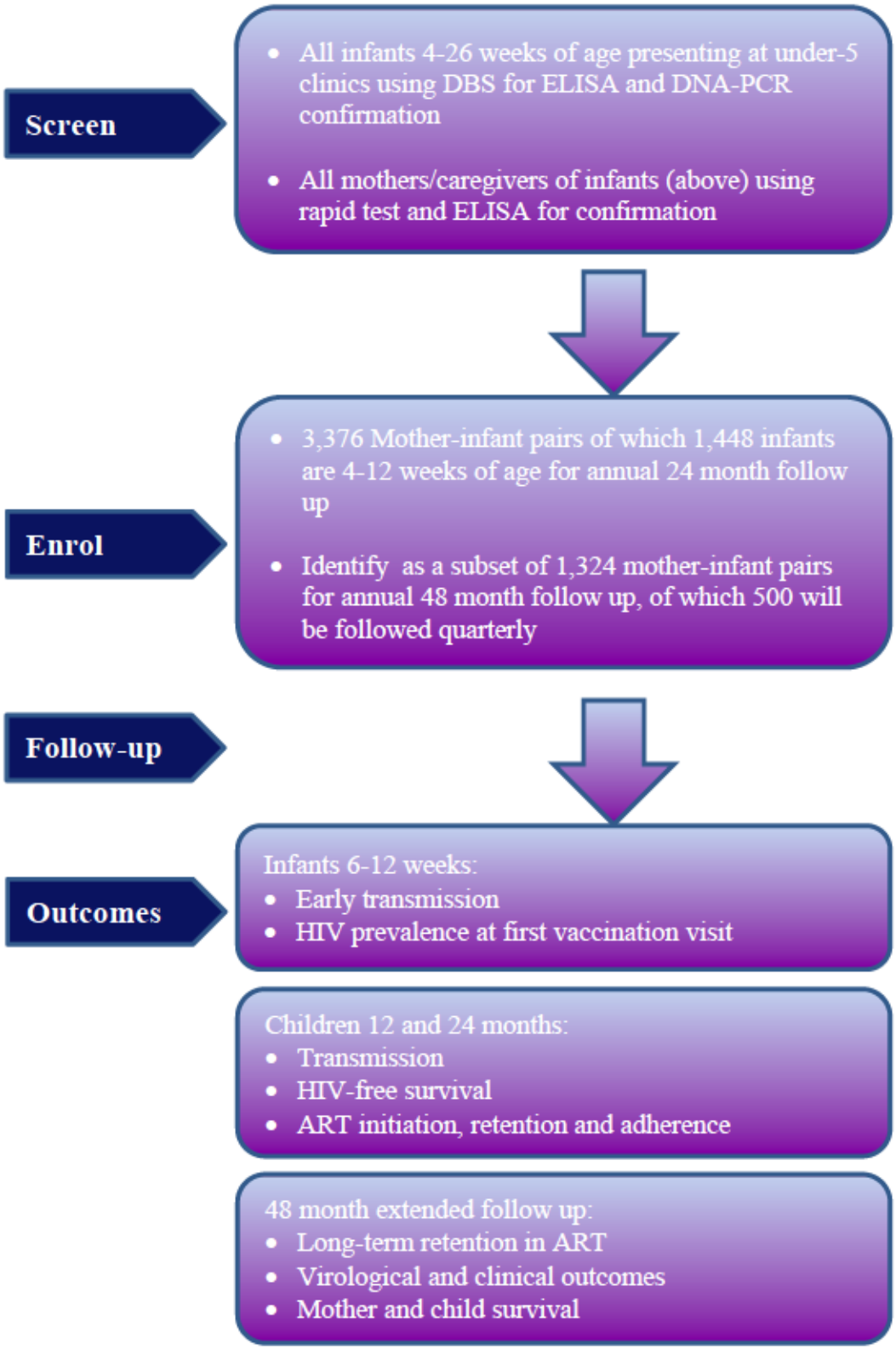
Using OpenEpi Exact Confidence Intervals for a proportion, requiring a precision of 2.5% for national estimate and 5% for strata estimate with a 95% confidence interval, and design effect of 2 nationally, and 1.5 at zonal level, sample sizes were calculated for 4-12 week MTCT and 24 month MTCT. To arrive at final sample sizes nationally and by strata, these were then adjusted upwards proportionally to reach the national required national sample size. The final national sample size for estimating 24 month MTCT was 3,376 infants, including at least 1,448 infants aged 4-12 weeks old to be able to estimate early transmission. The total number of infants to be screened at under-5 clinic is 36,963. Additional cohorts may be enrolled in subsequent years.

In order to monitor viral suppression amongst mothers of enrolled infants, a sub-sample of the mother-infant pair cohort will be followed for 48 months. It is unknown what viral suppression at 48 months will be, so 50% was used for sample size calculations. In addition, LTFU may be as high as 50%. Using the same method in OpenEpi as the previous sample size calculations, and a design effect of 2.0, we estimate we will need to enroll 1,324 mothers into the extended follow-up study cohort to arrive at a national estimate with 5% precision and a 95% confidence interval. For the extended follow-up participants, a subset of facilities selected by PPS (shown in Appendix 1) will only enroll the 48-month extended follow-up participants and not 24-month participants, for ease of implementation.

A sample of 500 mother-infant pairs is estimated to be needed for the enhanced follow up, which will allow estimation of the occurrence of adverse outcomes (a composite of side effects and morbidities, expected to be around 30% annually) with 5% precision and a 95% confidence interval. This sample of facilities was purposefully sampled across the geographical strata.

2.5 Schematic overview of evaluation

Figure 1. Schematic overview of Evaluation



3. National guidelines and M&E tools for patient care across the PMTCT and ART continuum

Data for the main outcomes of this study will be collected from the nationally standardized tools utilized by the Malawi MOH in routine HIV and MCH services delivered to patients. The Malawi ART and PMTCT programs have been integrated and pre-ART care added to services in 2011. The revised national program and revised monitoring and evaluation (M&E) tools strengthen the continuum of care for all HIV-infected persons, with a particular emphasis on following pregnant women through ANC and identifying and enrolling their HIV-exposed infants into care primarily at maternity or under-5 clinics.

With the integration of ART and PMTCT, MOH has advised all health facilities to provide ART and exposed-infant follow-up care in ANC/MCH settings during the pregnancy and breastfeeding periods wherever possible.

At the time of identification as HIV-infected, a pregnant woman is enrolled into the ART program using the ART register, an ART Patient Card is opened and she is assigned a unique ART number. Information collected on the ART Patient Card includes clinical stage at ART initiation, HIV testing history and additional clinical parameters including ART regimens, TB status, adherence measures, CPT, family planning methods, CD4 at initiation and viral load. Key identifying information on this card includes the woman's name, address, phone number, and ART registration number. The ART registration number is recorded in the patient-held national health passport. Summarized HIV-related information is also recorded in the integrated ANC/PMTCT Register.

All ART patients are seen monthly for the first 6 months and then every 3 months thereafter if stable and adherent. In addition, guidelines state that viral load monitoring of all ART patients will be done at 6, 24 and 48 months after ART initiation and then every 2 years thereafter.

According to national guidelines, all HIV-exposed infants should be registered for exposed infant follow-up in the HIV Care Clinic before discharge from maternity. Additionally, all infants attending under-five clinic for their first vaccination visit beginning at six weeks of age should be routinely screened for HIV exposure using either the mother's health passport, or the child's, if issued at delivery. If exposed, the child is referred to the HIV Care Clinic (HCC) for follow-up and a Pre-ART HIV-exposed infant Card is opened, the child is assigned a unique HCC number, and DBS is collected from the infant for PCR testing.

All infants enrolled in HCC are started on cotrimoxazole preventive therapy (CPT) and followed until a final HIV diagnosis is made. Key identifying information on the Pre-ART HIV-exposed Child Card includes name, address, phone number, mother's ART registration number and infant HCC number. The infant's HCC number and the maternal ART number are also documented in the patient-held health passport.

Following PCR testing at 6 weeks, national guidelines recommend HIV rapid testing at 12 and 24 months for all HIV-exposed children in follow-up AND a confirmatory rapid test for those who have already initiated ART due to presumptive HIV infection. Malawi's national HIV guidelines recommend all women breastfeed through 24 months of age regardless of HIV status.

All HIV-infected infants and children aged 24 months or less are eligible for ART. At the time of identification as HIV-infected, infants and children are enrolled into the ART program using the ART register, a Pediatric ART Patient Card is opened and they are assigned a unique ART number. Information collected on the ART Patient Card includes clinical status at ART initiation, HIV testing history and some clinical parameters including ART regimens, TB status, adherence measures, CPT, CD4 at initiation and viral load. Key identifying information on this card includes the child's name, address, guardian name, phone number for the patient and the guardian, and ART registration number. The ART registration number is recorded in the patient-held health passport. Stable pediatric ART patients are followed up on the same schedule as adults.

The M&E tools utilized by the national program include:

- ANC Register with integrated PMTCT data (Appendix 4).
- ART Register (Appendix 5)
- ART Patient Card (>25kg) (Appendix 6)
- ART Pediatric Patient Card (<25kg) (Appendix 7)
- Pre-ART HIV-exposed Child Card (Under 24mos) (Appendix 8)
- ART Quarterly Facility Reporting forms (Appendix 9)
- Under-5 Register (currently under revision by MOH)

4. Study Instruments

While utilizing the existing MOH patient care process and M&E tools as the primary data source for the study, additional activities and associated tools will be needed to implement and monitor study progress.

4.1 Screening, consent and questionnaires

Consent will be done prior to any blood draws for all mother-infant pairs screened for enrolment in the study. This one consent form has separate sections based on the chronological steps of the study: Screening, enrolment of infants for 24 months, and enrolment of the mother-infant pair subsets for the 48-month extended follow-up. Each consent form will be used multiple times during the course of the study and the date and participant signature will be included at each section.

The reading level of the consent form is elementary/primary school level. For those who cannot read, the consent form will be read to them by the counselor. The wording for the consent form has been simplified as much as possible. Acronyms are used in

place of the completely spelled out phrasing, as the general public in Malawi has been heavily sensitized to the terms "CD4", "ART", "PMTCT", "MOH" and "EID". This will be verified during the pilot of the study, and amended if necessary.

There will be one questionnaire form used for both enrolment and follow-up visits. The initial questionnaire will collect information not available on the maternal ART card or infant under 24 months card or pediatric ART card, and will take up to 20 minutes. Information collected includes antenatal care number and site, partner testing, HIV and ART status. A separate questionnaire will be used for the smaller subset of mother-infant pairs who will be followed through to 48 months. This questionnaire will obtain information about intercurrent morbidities, side effects, recurrent pregnancies and outcomes, and use of family planning.

4.2 Study register

The study register will be a quick reference tool for the site supervisor to document test results and identify children due the current month for a follow-up visit, those who have not returned for a scheduled visit, or who have not yet received testing or their test results. It will also document the date on which community follow-up was requested. The register will include name of infant, name and ART ID number of mother, child's study ID number, exposed infant follow-up number, contact details, and date of birth. This register will record infants by their birth cohort and include for each birth cohort page, an additional tabbed page recording all community tracing activity outcomes for each individual.

4.3 Testing logbook

This logbook will record details of each sample sent to the central laboratory for testing, date of return of result to site as well as date when result entered into study registers. This will be used by the site study coordinator to track all samples and so that he/she can know which samples need to be followed-up on.

4.4 Study labels

A set of barcode labels will be created for each mother-infant pair. These labels will be applied to the following:

a) Study register
b) Maternal ART record
c) Maternal health passport
d) Pre-ART HIV-exposed Child Card
e) Infant health passport
f) Questionnaires (includes consent form)
g) Maternal and infant DBS samples
h) Laboratory requisition forms accompanying DBS to the central laboratory
i) Laboratory result forms being returned to sites

j) Community follow-up form

A record will be kept of which bar codes are distributed to which facility, thereby facilitating the reporting of results to sites.

4.5 Extended Follow-up Register

The extended follow-up register for mother's being followed over 48 months. It includes the mother's contact information and viral load, CD4 and Hepatitis B testing results and outcomes at each testing point.

4.6 Site Supervision Form

The Site Supervision Form will be completed by the Initiation Team following successful initiation of the site as a study site and completion of the first week of enrollment. This report form includes names and contact details for trainers and participants in training sessions, training activities completed, any issues encountered during training and/or the first week of enrollment, together with any corrective actions taken. The form will also be utilized by Supervision Teams when they visit sites to conduct data abstraction and data quality checks.

4.7 Community tracer logbook

This logbook 19) will be held by the community tracers and will record the date they received the referral, contact information for the study participant to be traced as well as the outcome of the tracing activity.

4.8 Community tracing form

All patients more than two weeks late for a visit will be followed-up in the community by a community outreach staff employed by the study. A community tracing form will be completed for each tracing activity conducted which will document the outcome of the activity and the current status of the patient who was traced.

4.9 Study database

Individual level data will be abstracted from the medical records and entered into a data entry program on site on a laptop on a quarterly basis by the supervision team, and uploaded into the study database. Data collected through interview of the mothers/caregivers will be recorded on (scannable Tele-form) paper questionnaires, and collected on a quarterly basis by the supervision team. The Tele-forms will be scanned and the data management team will verify and validate data before each form is uploaded into the main study database. This database (hosted at the HIV department in the MoH) will be password-protected and will not contain names. An additional secure backup of the database will be maintained.

5. Screening for HIV Exposure

As a result of discrepant HIV prevalence reports in the ANC program, ANC surveillance and DHS 2010, the Ministry of Health has concerns regarding the sensitivity of the

current rapid test algorithm, particularly in high burden settings such as ANC and Maternity. A new testing algorithm is being finalized at present, and to ensure the new algorithm is performing to expectations in the field, retesting of mothers will be an intensive focus in the under-5 clinic (as per the national provider-initiated testing guidelines), with all rapid test results confirmed through ELISA testing. This approach will also ensure that HIV-infected women previously missed at ANC or Maternity will be correctly identified for ART initiation, and their infants' true HIV exposure status is established. It will also identify women previously identified as positive who are uninfected.

Study staff and clinic staff will work together to identify HIV-infected mothers and their HIV-exposed infants age 4-26 weeks attending the under-5 five clinic. Refusal rates and reasons for refusal will be recorded (in a separate register) as part of the main study . Refusal rates and reasons will be monitored over the course of the study to examine variation and issues related to clinic and/or individual data collectors as a component of study management. Care will be taken to ensure that known HIV-positive mothers who refuse to participate in the study understand that their refusal does not negatively impact their access to, or quality of, care.

For all consenting and eligible mother-infant pairs:

- All mothers and caregivers with unknown HIV status or a previous negative or indeterminate rapid test result will be offered a rapid HIV test the same day
- All mothers regardless of their HIV status will be offered DBS for ELISA testing; all ELISA results which are discordant to rapid-test results will be reported back to the mother at the next visit
- All infants regardless of mother's HIV status will have a DBS collected for ELISA testing at the central laboratory to determine *HIV-exposure status*; for those determined to be exposed, the DBS sample will then undergo DNA PCR testing to determine HIV-*infection* status
- In the unlikely situation that the infant and mother's ELISA test results are not biologically feasible (negative mother with exposed infant, or positive mother with unexposed infant), then the situation will be discussed within the study team and the MOH Department of HIV and AIDS to determine next steps

Infants not accompanied by their mother

For all infants not accompanied by their mother at the screening visit, MOH protocol will be observed and the infant will receive a rapid HIV test to determine exposure status and will also have a DBS for ELISA testing. The caregiver will also be offered a rapid test. In the unlikely event that the mother is alive but not present, the child is not eligible for study enrolment. If the mother has died and the child is confirmed as HIV-exposed, the child can be included in the study cohort.

6 Testing for HIV Infection

6.1 HIV infection in infants age 4-26 weeks

For HIV-exposed infants less than 26 weeks of age, infection status will be determined by the running of DNA PCR tests in the lab after a positive ELISA result is identified. Infants with a positive PCR test are HIV-infected. Infants with a negative DNA PCR are HIV-uninfected but still HIV-exposed (if breastfeeding), and parents/caregivers will be counseled to continue attending HIV exposed infant follow-up clinic.

6.2 HIV infection in infants at 12 and 24 months

For 12 and 24 month follow-up visits, infection status will be determined by rapid HIV test according to national guidelines. DBS will also be collected from all infants receiving rapid HIV testing, regardless of rapid test result, to undergo confirmatory ELISA testing at the central laboratory. DBS that are ELISA positive will subsequently undergo DNA PCR testing. DBS that are ELISA negative will not undergo further testing.

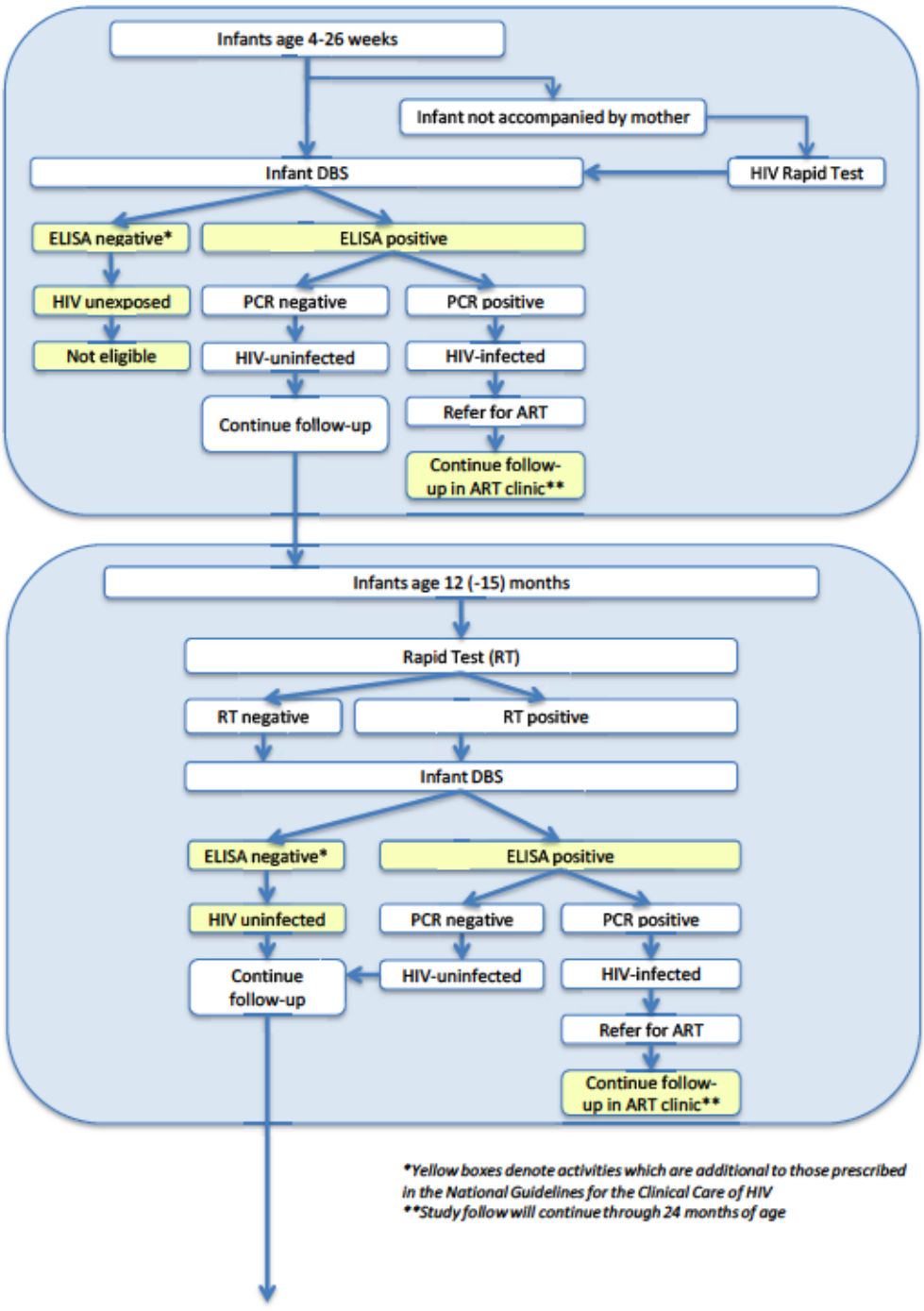
Infants may present for the 12-month test at an older age, and this study testing algorithm will be used for all study-enrolled infants presenting for HIV testing when aged 12-15 months of age, allowing for validation of Malawi's young child testing algorithm.

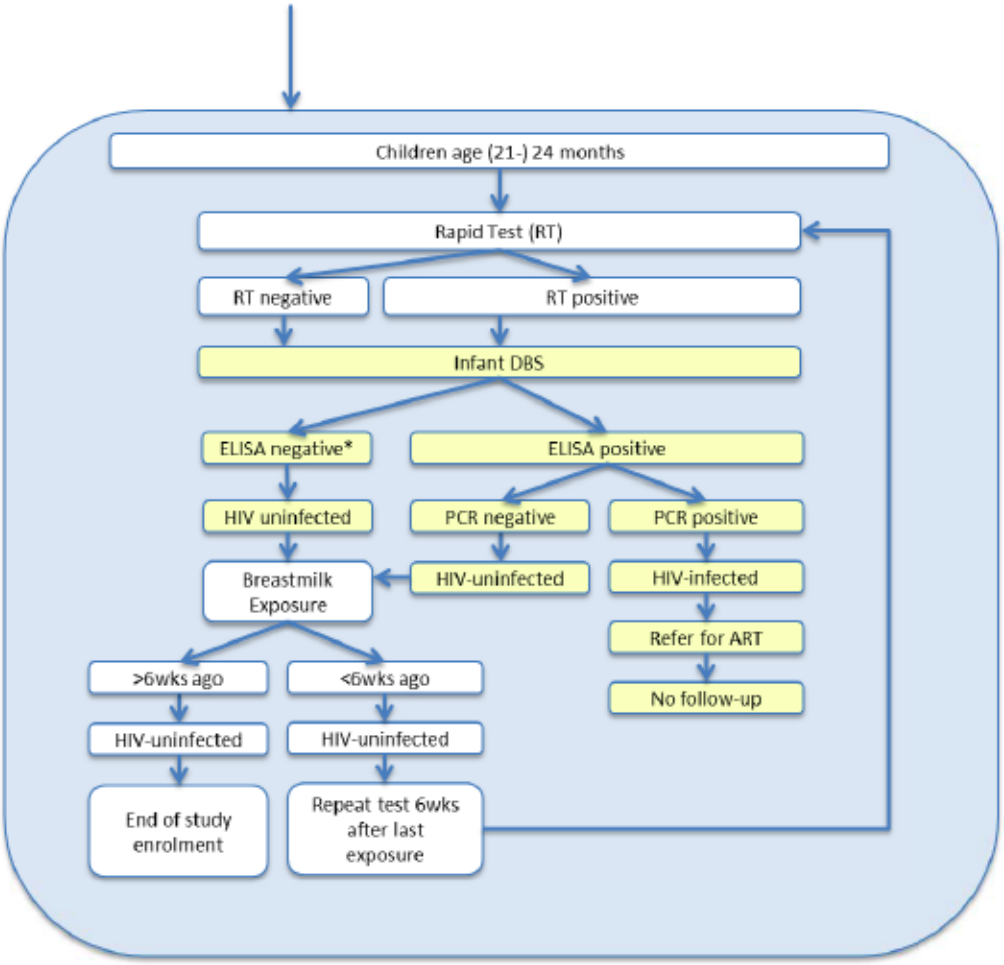
Infants may present for the 24-month test at an older age; therefore this testing algorithm will be used for study-enrolled infants presenting for HIV testing aged 24 months and above.

For infants presenting for the 24 month test, if last exposure to breast milk was less than 6 weeks previously, the child will be determined to have ongoing exposure and the mother will be asked to return with the child for repeat rapid HIV testing at least 6 weeks after weaning, and to maintain follow-up in the HIV exposed child follow-up clinic.

Immediate clinical care decisions will be based on a positive rapid HIV test result, without waiting for ELISA or DNA-PCR results: Children aged 12 or more months with a positive HIV rapid test will be assumed to be HIV-infected and enrolled in ART care services as per MOH guidelines, but study follow up will continue untill 24 months. The following figure describes the infant testing algorithm for this evaluation.

Figure 2. Infant Testing Algorithm





6.3 Sample collection and transportation

Rapid testing at the site will be conducted according to national PITC guidelines. Infant DBS, obtained using a heel prick, will be collected on a Guthrie card and maternal/caregiver DBS will be created using blood collected in an EDTA microtube from finger prick. Following drying, the filter paper (with the DBS) will be inserted into a self-sealing envelope with desiccant. DBS will only be collected by study or clinic staff trained in the procedure. Training will include fully informing field researchers of the risks, the need to take universal precautions and on procedures related to accidental needle-prick injuries. DBS will then be transported to a central laboratory, along with laboratory requisition forms, for logging and analysis.

All testing and sample transportation will be conducted according to the national laboratory guidelines. Quality control activities will be conducted in these laboratories throughout the study on a regular basis as part of system strengthening activities. The use of samples for future testing will require approval from CDC and NHSRC (the national IRB).

6.4 Return of results and scheduling return visits

Results from testing at the central laboratory will be returned to sites within 4 weeks of collection to facilitate study flow in alignment with the routinely followed EPI schedule. At the time the DBS sample is collected for DNA PCR testing and/or ELISA testing and/or maternal VL measurement, lay workers/clinic staff will schedule a single appointment for the parent or legal guardian to return to the clinic for laboratory test results. For infants, as per MOH guidelines, attempts will be made to align this follow up visit with the next EPI scheduled visit. If that is not possible (i.e., if the next EPI visit is several months away, project staff will work to find a suitable time for a follow up visit. At the time of maternal testing (ELISA and/or VL), mothers will be told that nobody else is allowed to collect the mother's results on her behalf.

All mothers and caregivers will receive the results of their own or their child's HIV rapid test on the same day the blood sample is taken during an individual post-test counseling session.

Legal guardianship is not routinely practiced in Malawi; health policy allows that any non-parent presenting at a health facility with a child has legal decision-making authority over the child, and can therefore collect any lab results for the child.

Study staff will not schedule visits for returning results of the mother's confirmatory ELISA testing. However, where there is discordance between the mother's rapid test result and the final ELISA result, staff will use the contact details provided for the study to follow-up the mother and provide them with the final result, counseling and referral to HIV care and treatment services.

6.5 Access to care and treatment

All HIV-exposed infants will be enrolled in the HIV Care Clinic if they have not already been enrolled at maternity. Newly identified HIV-infected breastfeeding mothers will be initiated on ART according to national guidelines. They will also be invited to participate in the study and those who consent will be followed up prospectively using routinely collected program data and interview.

At the time of enrollment, information about mother-infant pairs will also be entered in the study register to facilitate tracking of mother-infant pairs as described in the section on Study Instruments. Lay workers and clinical staff will also ensure that an Exposed Infant Patient Card is begun for each HIV-exposed infant identified and that all HIV-positive mothers who are newly diagnosed and/or who are not currently enrolled in HIV treatment are registered at the ART clinic where an adult ART card will be opened and the mother will be assigned an ART number. Mother's ANC number will also be documented in the "Notes" section of the exposed infant follow-up card, and the ART card.

All HIV-infected infants and children aged 24 months or less will be initiated on ART according to national guidelines; a pediatric ART Patient Card will be opened and the child will be assigned an ART number. Follow-up of these children will be continued through 24 months of age.

6.6 Laboratory Testing

This study will use the standard screening and confirmatory testing used by Ministry of Health. At present the rapid test algorithm is serial, with Determine as a first test, Unigold as a confirmatory, and Bioline as a tie-breaker. Since the recall of Bioline, MOH has issued a circular to all districts to implement a repeating of test 1 and 2 for discordant results.

All lab testing for this study will be aligned with international standards. In preparation for the study, a lab consultant will be tasked to develop SOPs for all laboratory activities. These SOPs will be tailored to fit with the laboratory contracted to support the evaluation. The draft SOPs for the laboratory will be submitted for comment to the Lab group in Atlanta, as well as to the Department of Diagnostics and Central Reference Lab at MOH.

6.7 Additional strategies to improve attendance/ retention within care and follow-up and strengthen data quality

National guidelines recommend monthly follow-up appointments for the first 6 months of all patients initiating ART and 3-monthly appointments thereafter as long as they remain stable. Mothers/caregivers will be informed that their exposed but uninfected infants will be offered repeat testing at 12 and 24 months of age.

This study will utilize additional strategies to strengthen adherence and retention among these women:

a) Study staff will escort all caregivers and infants between different services to reduce patient loss during referral processes

b) A site-based study coordinator will be identified from existing health care workers if possible at each site to coordinate study implementation at their site and receive an additional stipend for this responsibility. At sites where this is not feasible, study staff will be employed to fill this role of site study coordinator

c) The site study coordinator will coordinate ongoing data quality review activities – this will include reviewing completeness of data tools completed by themselves and program staff and providing ongoing feedback. In particular, study staff will check Exposed Child Cards for missing maternal ART and ANC numbers. When these numbers are missing, the space on the form will be ink highlighted as a visual prompt for completion at the next patient visit.

d) Site initiation teams will support the study start-up phase and conduct frequent visits to ensure study protocol is being followed

e) Site supervision teams will conduct quarterly data quality reviews during the ongoing follow-up phase, and give feedback to the study and program staff

f) Study staff will trace patients who are more than 2 weeks late for a study visit. Each defaulter will receive two follow-up visits and then a final outcome recorded if they do not return to care. As routine clinical care is more frequent, the active follow-up of patients lost to the study will not heavily influence loss from routine clinical care.

6.8 Training for study personnel

Study staff will be employed to support program staff in achieving the study objectives. The duties of those study staff include: screening mother-infant pairs for study eligibility; performing medical chart abstraction; collecting dried blood spots from infants and mothers/caregivers enrolled in the study; provision of rapid testing to eligible consenting mothers and caregivers and children aged 24 months; escorting all caregivers and infants between different services; ensuring all records are correctly filled out and labeled with the unique study barcode number; conducting ongoing data quality reviews; conducting active community-based tracing to encourage mothers and infants who are late for appointments or lost to follow-up to return to care.

Prior to study implementation, all site and study staff will receive training on the following areas:

a) Relevant aspects of ethical conduct of research including the need to maintain the confidentiality of patient information prior to the start of all data collection activities

b) Revised National Guidelines on Clinical Management of HIV in Adults and Children

c) Purpose and design of evaluation, with clear descriptions of the different cohorts

d) Screening mother-infant pairs for eligibility for enrollment into Care using the integrated screening, consent, questionnaire form for HIV-exposed mother-infant pairs

e) Completion of Study Register

f) Rapid HIV testing in mothers and infants (see below)

g) DBS collection from infants and adults

h) Viral load measurement protocol for study

i) Completion of program data tools, specifically the Under 24 months Exposed Infant card and the Adult ART card.

j) Completion of Community tracing form

Prior to study implementation, evaluation supervisors and coordinators will receive training on the following areas:

a) Relevant aspects of ethical conduct of research including the need to maintain the confidentiality of patient information prior to the start of all data collection activities.

b) Revised National Guidelines on Clinical Management of HIV in Adults and Children

c) Purpose and design of evaluation

k) Screening mother-infant pairs for eligibility for enrollment into care using the integrated screening, consent, questionnaire form for HIV-exposed mother-infant pairs

d) Completion of Patient Register

e) Completion of program data tools, specifically the Under 24 months Exposed Infant card and the Adult ART card

f) Use of study barcode labels

g) Correct procedures for collecting and transporting DBS samples

h) Purpose and role of supervisors and coordinators including quarterly supervision visits, data quality assessments and data abstraction methods

i) Use of the community tracing form

When relevant, staff will receive training in the national HTC guidelines, using the national HTC training curriculum as per MOH guidelines.

6.9 Data collection

6.9.1 Abstraction from medical charts

Mother-infant pairs enrolled in the study will be followed prospectively using routinely collected program data. Information from the Exposed Infant Patient Card and the mother's ART Patient Card will be abstracted by supervision staff on their quarterly visits.

Quarterly supervision teams will abstract data from the paper tools and enter into a data entry program on site using a laptop or other electronic device. As surveys are completed they will be systematically uploaded to the central database In sites with the Baobab Database System, the required information will be exported from the Baobab system and included in the study database.

6.9.2 Interviews with mothers and caregivers

Mothers/ caregivers will be interviewed at enrollment and at each subsequent infant test and mother test points. Completed questionnaires will be stored at the study site in a locked filing cabinet. The quarterly site supervision visits will provide an opportunity to collect all questionnaires and take them to the study headquarters,

where Tele-forms will be scanned and data entry clerks will verify and validate data into the study database.

6.9.3 Community follow-up

Site staff will conduct community-based tracing activities on a monthly basis, trying to find patients who are more than 2 weeks late for a study visit. They will use a tracing logbook to record all the tracing referrals they receive, as well as the outcome of the first and second follow-up visits. In addition, a tracing form will be completed for each patient they attempted to trace. These forms will be stored in a locked cabinet and collected each quarter for secure data entry into the study database.

6.10. Quality control/quality assurance measures

6.10.1 Program and study supervision

The HIV and AIDS Department in the MOH conducts integrated quarterly site supervision visits to every site in the country, in order to review data quality and completeness, and patient and clinic management. Sites with excellent performance in patient and clinic management, including completion of ART registers and master cards and correct cohort analysis are awarded a certificate of excellence. Feedback to sites on areas of weakness is provided at the time of the site supervision visit. Investigators will use these quarterly site supervision visits to support the evaluation in conducting system strengthening activities, ensuring data quality and completeness and optimal patient and clinic management. Significant issues identified during these routine MOH supervision visits will be followed up by evaluation supervisors and coordinators to ensure weaknesses are addressed, thus strengthening national capacity for PMTCT program implementation.

At each site, MOH program staff will be conduct additional study-related duties for which they will receive a monthly stipend for the duration of the study. It is anticipated that this will not adversely affect the provision of routine services at the site as the study relies on implementation of routine guidelines with some additional activities. However, where needed, additional staff will be hired by MSH/DI to support study implementation. Every site will have an MOH site study coordinator who will ensure that HIV care and treatment services are implemented according to national guidelines, all infants are being screened for HIV-exposure correctly, infants and mothers receive HIV testing according to national guidelines, DBS are collected appropriately, mothers and infants receive HIV care and treatment services in a timely manner, medical record cards are filled out correctly. In addition, the MOH site study coordinator will ensure that additional study-specific activities are also conducted correctly: infant and maternal DBS for ELISA testing, maternal DBS for VL testing, consent and interviews of mothers and caregivers, and community tracing for all patients who are more than 2 weeks late for an appointment.

The study will employ zonal study coordinators for each stratum who will coordinate overall field work operations and trainings. Site study coordinators will collaborate with the study zonal coordinator. The zonal study coordinators will organize with the MOH and Implementing Partner(s) quality control visits during study implementation to check screening procedures for infant HIV exposure, maternal and infant cards for data completeness and quality, and overall adherence to study protocol.

The use of barcode ID labels is intended to minimize the risk of multiple enrollments of the same infant into the study. No names will be entered into the evaluation database and so investigators are dependent on checks on the HCC number and maternal ART number at the time of registration and enrollment. Investigators will not be able to identify multiple enrollments of the same infant who has previously been issued an ART number but re-presents as a new patient who has never been registered at ART. The use of barcodes will also facilitate the removal of data and samples for any individuals who request to withdraw from the study. Withdrawal from the study can occur at any time the participant requests, and no further lab investigations will be done on those samples. The participant will be reminded that samples and data already collected are not identifiable; however if previous analyses and/or data already collected is still requested to be withdrawn, the participant's wishes will be respected.

6.10.2 Study initiation teams

Study initiation teams (consisting of investigators, zonal study coordinators, district PMTCT coordinators and district Laboratory coordinators) will be trained to lead study site staff training prior to study implementation, and will remain at the site during the first couple of days of enrollment to address any issues that may arise, and will conduct frequent visits thereafter. The teams will monitor all aspects of the study including: screening and enrollment; sample collection, packaging and delivery to central laboratories; provision of rapid testing and counseling; completion of study tools and quality of data; linkages to HIV care and treatment services including escort by study staff; patient flow. Study initiation will be reported on initiation site supervision form for each site.

6.10.3 Study supervision teams

Study initiations teams will become study supervision teams once recruitment is ongoing. Study supervision teams will visit study sites initially at least on a quarterly basis. During these visits, supervisors will meet with the site-based study staff and program staff, discuss and resolve any issues that have arisen during the previous quarter and resolve. Supervisors will review data quality and conduct data abstraction from the maternal and infant medical records, using laptops. Supervisors will electronically send abstracted data to the data manager on a daily basis. These visits will be documented on the site supervision form.

7. Data handling and Analysis

7.1 Data Ownership

All data will belong to Ministry of Health. Primary data sharing will be with implementing partners for analysis and reporting, as per sub-contracting terms of reference. Further data sharing will be at the discretion of the Ministry of Health.

7.2 Data analysis plan

Data analysis will be conducted in SAS (or similar appropriate statistical package) by CDC statisticians and implementing partner(s) in consultation with the study coordinating committee.

Basic frequencies and 95% confidence intervals (for categorical data) and means and standard deviation (for continuous data) will be used for descriptive analysis of all data. Analysis will be conducted to test associations of cohort characteristics with outcomes. All results will be adjusted for clustering effects and weighted as appropriate for proportionate sampling methodology.

a) Estimates for each primary objective will be produced by cohort

b) Primary outcomes will be compared between cohorts; study power will be noted for these comparisons, as the study was primarily powered to measure outcomes in a single cohort

c) 12 and 24-month outcomes of a cohort (censoring etc): MTCT rates at 4-12 weeks, 12 months, and 24 months will be estimated using survey analysis procedures to account for clustering, including 95% confidence intervals. Tests of association, using these procedures, will be done against HIV status of the infant at each time point. Lastly, logistic regression of survey data will be done to examine all predictors

d) Survival analysis: We will test retention outcomes (alive and HIV-free, HIV positive, LTFU) against selected characteristics using a Cox proportional hazards model for survey data, and assess risk factors for mortality and defaulting by Kaplan-Meier survival and cox regression analyses

e) Cohort analysis to describe morbidities, toxicities, virological ART failure and resistance patterns, non-adherence, growth of infants, HBV prevalence (and HBV treatment outcomes in those infected), utilization of family planning and recurrent pregnancies and outcomes (thereof)

f) HIV rapid testing validation: The variation between rapid test results and ELISA test results will be measured using pooled data from a complete cohort, and then reviewed for clustering or significant variations at site, district and zonal levels.

7.3 Addressing patients who are lost to follow-up

Previous evaluations of PMTCT effectiveness using a prospective cohort approach have been conducted in Cameroon and Kenya (29, 30) and both experienced high follow-up losses. Although it is anticipated that there will be a large loss-to-follow-up (LTFU) rate among the enrolled cohort, which could lead to bias, investigators have taken this into account during sample size calculations.

Patients not returning for care and treatment over time creates a significant barrier to the accurate assessment of survival outcomes among patient cohorts. Study staff will go into the surrounding community to actively trace patients who are more than two weeks late for a study visit. Outcomes of these tracing activities will be recorded on a tracing form and collected quarterly for entry into the central study database. Patients who have not returned to care after two follow-up visits will be classified as "lost-to-follow-up".

7.4 Defining Testing outcomes

The primary testing outcomes of the study will be:

a) HIV transmission rates at 4-12 weeks, 12 months and 24 months of age

b) HIV-free survival at 12 and 24 months

c) Viral suppression in mothers at 6, 12, 24, 36 and 48 months post-ART initiation

Table 2: Primary and secondary testing outcome definitions

Estimates for the secondary outcomes are unknown. Estimates for the primary outcomes are listed in the sample size calculation in Appendix 2.

Outcomes	Numerator	Denominator	Stratify by	Source of data
Early transmission rate among HIV-exposed infants aged 4-12 weeks	Number of infants with established exposure and +ve DNA PCR test	Number of +ve ELISA	zone	Infant DNA PCR and ELISA results recorded at lab and study site.
Infant prevalence (aged 4-12 weeks)	Number of infants with +ve DNA PCR	Number of samples tested	zone	DNA PCR results recorded at lab and site.
Overall transmission rate among infants aged 12 months	Number of infants with established HIV exposure and a positive DNA PCR test between 12-15 months of age	Number of infants with established HIV exposure	zone	DNA PCR and ELISA results recorded at lab and study site.
Overall transmission rate among children aged 24 months	(Infants with established HIV exposure and positive DNA PCR test between 12-15 months) + (Infants with established exposure and	Infants with established HIV exposure	zone	DNA PCR and ELISA results recorded at lab and study site HIV rapid test results conducted at site

	positive ELISA test from 24 months)			
HIV-free survival at 12 months *(with censoring)*	Infants who are alive, HIV-uninfected, retained within care at 12 months	Infants who are alive and retained within care at 12 months (infants and children who have died or defaulted will be censored)	Zone	DNA PCR and ELISA results recorded at lab and study site. HIV rapid test results conducted at site
HIV-free survival at 12 months *(no censoring)*	Infants who are alive, HIV-uninfected, retained within care at 12 months	Infants who are alive and retained within care at 12 months (infants and children who have died or defaulted will **NOT** be censored)	Zone	DNA PCR and ELISA results recorded at lab and study site. HIV rapid test results conducted at site
HIV-free survival at 24 months *(with censoring)*	Infants who are alive, HIV-uninfected, retained within care at 24 months	Infants who are alive and retained within care at 24 months (infants and children who have died or defaulted will be censored)	zone	DNA PCR and ELISA results recorded at lab and study site. HIV rapid test results conducted at site
HIV-free survival at 24 months *(no censoring)*	Infants who are alive, HIV-uninfected, retained within care at 24 months	Infants who are alive and retained within care at 24 months (infants and children who have died or defaulted will **NOT** be censored)	Zone	DNA PCR and ELISA results recorded at lab and study site. HIV rapid test results conducted at site
Viral Suppression	Less than 5,000 or 1,000 copies per mL at 6, 12, 24, 36 and 48 months post-ART initiation	Number of mothers tested	National	DBS collected at site, results recorded at lab and study site
Survival rates of mothers and infants at 12, 24, 36 and 48 months	Mothers who are alive at 12, 24, 36 and 48 months Infants who are alive at 12, 24, 36 and 48 months	Number of mothers in subset Number of infants in subset	National	Data collected at study visit
Rates of non-adherence and resistance patterns in those with virologic failure	Mothers with adherence <95% Mothers with virologic failure	Number of mothers in subset	National	DBS collected at site, results recorded at lab and study site

Rates of comorbidities, toxicities, utilization of family planning and recurrent pregnancies, and associations of clinical outcomes with maternal and infant characteristics	Number of comorbidities documented Number of mothers using FP Number of mothers becoming pregnant again during follow-up Clinical outcome of interest	Number of mothers in subset Number of mothers in subset Number of mothers in subset Number of infants or mothers with the clinical manifestation of interest	National	Data collected at study visit

7.5 Information management

Study-specific data collection will be conducted using the following paper data collection forms:

a) Integrated screening, enrollment, consent form
b) Enrolment/Follow-up questionnaire for 24 month cohort
c) Follow-up visit questionnaire for extended 48 month cohort
d) Laboratory requisition forms
e) Quarterly supervision report forms
f) Initiation team report forms
g) Community follow-up form

At sites with Baobab EDS, patient data from maternal and infant medical cards will be exported from Baobab to the study database, thus removing the need for the use of quarterly data abstraction forms at these sites. At sites that do not have Baobab EDS, data abstraction from maternal and infant medical cards will be conducted by the quarterly supervision staff who will enter the data into a database using a laptop or handheld electronic device.

In addition, hard copy study registers and logbooks will be used by study staff to track patients and samples and record outcomes, including tracing activities:

a) Main study cohort register
b) 48 month follow-up cohort register
c) Register for additional infants of 48 Month cohort of mothers
d) Testing log book
e) Tracing log book

When creating a database for the evaluation, investigators will ensure that data can be shared between the evaluation database and the Baobab database. Where that is not possible, quarterly supervision teams will abstract data from the paper tools at the sites directly into a data base on a laptop or other electronic data collection system. Where possible, investigators will make use of the existing touchscreen Baobab ART electronic data system (BART II).

All integrated screening, enrollment and questionnaire forms, additional consent and questionnaire forms, and registers will be kept in a locked file cabinet at the study site and will only be accessible to study staff and clinic staff. All logbooks, forms, and patient registers will be securely stored as described above until data entry, cleaning, and analysis is complete; at that point all hard copies will be destroyed.

Initiation team report forms and Supervision team report forms will be taken to Lilongwe after completion of the visits, where they will be stored in a locked file cabinet and only be accessible to study staff.

7.6 Laboratory information management

Laboratory HIV test results (infant and maternal) will be sent electronically from the central laboratories to the data manager. The unique study barcode ID number will be used to link infant and maternal test results to individual records within the study dataset.

A master copy of all HIV test results conducted during the enrollment phase of the study will be created. This will be used to identify the cohort of HIV-exposed infants to be followed-up. Study sites will receive their test results through the usual methods by which all sample test results return to the site. However, each site will also receive the master-copy of the HIV test results at the end of enrollment in order to cross check completeness of the study register and patient records.

7.8 Data entry

All paper data collection forms will be transformed into scannable Tele-forms to reduce human error during data entry. . Patient information will be entered into this system using the unique study ID number (barcode) assigned to each participant. No patient names will be entered into this system. Data collectors will not have access to the electronic database and study investigators will not have access to personal identifying information of the study participants.

Laboratory HIV test results (infant and maternal) will be sent electronically from the central laboratories to the study data manager. Clinical data (from the maternal ART card, infant pre-ART card and pediatric ART card) will also be electronically exported to the study data manager. The data manager will link electronically received data to database records using the unique study barcode ID number.

The data manager will monitor data quality, completeness and accuracy as it is entered into the database, sending queries to the site-based study coordinators. All queries which cannot be resolved by the site-based study coordinator will be addressed by the quarterly site supervision teams.

7.9 Master lists generated by study database

The study database will be used to generate the following master lists:

a) All enrolled infants and caregivers by site: this will be shared with each site coordinator and supervisors conducting quarterly visits for data abstraction. Site coordinators will use this list to crosscheck against the infants they have listed in the patient register. Supervisors will use this list to identify which records to abstract data from

b) All infants due for 12 and 24 month testing and all mothers due for 36 and 48 month testing: active community-based tracing will be conducted based on those who are late for appointments

c) All mother-infant pairs (the subgroup within the extended cohort) due for quarterly visits

7.10 Bias

Potential bias in this study includes the following

a) Coverage of the 1st DTP vaccination visit was estimated to be 97% in the 2010 Malawi DHS. However, it is unclear at what age infants attend for this visit and how successful the HIV program is in identifying HIV-exposure status of infants at this visit or even subsequent immunization visits. Investigators believe that including all infants aged less than 6 months when attending any under-5 clinic will create a cohort reasonably representative of the population of HIV-exposed infants for calculation of transmission rates and outcomes at 12 and 24 months of age

b) Stillbirths and neonatal deaths will not be included in this study leading to a potential under-estimate of HIV transmission and over-estimation of HIV-free survival

c) Anecdotally, clinic staff report that most women and caregivers accept HIV testing for their infant through collection of DBS for DNA PCR testing. Since routine screening of mothers for HIV status during the breastfeeding period is not yet systematically implemented in Malawi, it is unclear what acceptance rates will be for HIV rapid testing, although over 95% of pregnant women in ANC accept an HIV test, and as this is the same population of women, similar high coverage is expected. Rates of refusal for HIV rapid testing of the mother and infant (where indicated) will be recorded.

7.11 Intermediate Reviews and Analyses

Data collection will occur over 4 years for the study. Intermediate data reviews will be conducted as investigators calculate the primary study objectives for infants aged 4-12 weeks, 12 months and 24 months. All findings of intermediate reviews and analyses will be shared with the MoH and stakeholders including the relevant national TWGs, the National AIDS Commission (NAC), the Office of the President and Cabinet (OPC), UNAIDS, UNICEF, WHO, and key implementing partners in country. In addition, papers for peer-reviewed journals and presentations for international conferences will be prepared.

7.12 Study Limitations

There are two main limitations to this study design.

Infants who do not attend under-5 clinics for well-child visits or who have died before attending an under-5 clinic will not be included in the cohort leading to a possible under-estimation of HIV prevalence and overestimation of the PMTCT program's effectiveness.

Study inclusion criteria for the prospective cohort allows for enrollment of infants aged 4-26 weeks attending a study-selected under-5 clinic. Since investigators have not limited study enrollment to a more restricted age range and time point there is

potentially a risk of multiple enrollments of the same infant. As described above, several procedures will be implemented to reduce this risk.

8 Ethical Issues

8.1 Enrollment and the consent process

Trained study staff will recruit eligible mother/caregiver-infant pairs attending an under-5 clinic. Each morning when mothers gather at the under-5 clinic, a group education session will be provided on the study. Women will be invited to participate in the study, and those agreeing will be given a card to indicate preliminary acceptance into the study cohort. Study staff will then consecutively escort each mother-infant pair to a designated study enrollment area with adequate privacy.

The study staff will then explain the purpose of the study, involvement of the study participant, risks and benefits of participation, the right to refuse or withdraw at any time, confidentiality processes and the implications of a positive test result. The study staff will also provide the written study description from the consent form to the participant which includes everything that was explained verbally. If the mother/caregiver understands and agrees to participate, the study staff will have the mother sign the consent form and provide an additional copy of the consent from to them.

Study staff will ensure that mothers who decline to participate are made aware that their infant should still be tested as part of routine care and that access to services for both themselves and their infant is not affected by their decision on whether to participate or not.

Written, signed, informed consent for all procedures in the study will be obtained from each eligible caregiver. Consent forms will be translated into the appropriate language at an appropriate reading level. These consent forms will also be back-translated prior to use to ensure accuracy and that the original information has been preserved throughout the translation process.

Informed consent will also be obtained to store the DBS for an indefinite period of time for use in other studies that seek to improve maternal and child health (e.g. HIV drug resistance surveillance), and from parents/ legal guardians to be contacted for participation in future follow-up studies looking at long term outcomes of pediatric HIV treatment.

Interviews will only be conducted after ascertainment of the mother and child's HIV status.

8.2 Access to HIV antibody Test Results and PCR Test Results

At the time of DBS collection, mothers/caregivers will be given a scheduled appointment to return for collection of results 4 weeks later. Approximately two weeks after a missed appointment, staff will go into the community to actively trace the patient.

All mothers, caregivers who receive a rapid HIV test will receive their HIV test results during an individual post-test counseling session on the same day as the blood sample is taken. For children who receive an HIV rapid antibody test, parents/caregivers will receive the infant's HIV rapid test result the same day as the blood sample is taken. Health policy in Malawi accords legal authority over any adult presenting with a child at a health facility. Therefore, lab results will be provided to the adult who brings an HIV-exposed infant to care.

For all infants and mothers/caregivers who undergo rapid HIV testing, a DBS will be collected for confirmatory ELISA testing at a central laboratory. These patients will not be asked to return to the site for results of ELISA testing. However, patients with discordance between the ELISA result and the rapid test result they received at the site will be followed up by staff to receive the final ELISA result, counseling and any appropriate referrals to HIV care and treatment services.

8.3 Confidentiality

A number of precautions will be taken to protect the confidentiality of the participants' information.

A unique study ID number will be assigned to each participant and inserted in the maternal ART record, maternal health passport, pre-ART HIV-exposed child card, infant health passport, consent forms, questionnaires, maternal and infant DBS, laboratory requisition forms accompanying DBS to the central laboratory, laboratory results forms returning to sites, community follow-up forms and study register for the purpose of data linking and tracking, and to provide results to parents/legal guardians.

All study staff will be trained in the ethical conduct of research including the need to maintain the confidentiality of patient information prior to the start of all data collection activities, and will sign confidentiality agreements. In addition, the electronic data entry system used to store the information from the medical chart abstractions will only include de-identified patient information. Patient information will be entered into this system using the unique study ID number assigned to each participant. No patient names will be entered into this system. Data collectors will not have access to the electronic database and study investigators will not have access to personal identifying information of the study participants.

The study register (Appendix 15) used by study staff to follow-up the mother-infant pairs will be kept in a locked filing cabinet and will only be accessible to study staff and clinic staff. Baobab data entry systems and database are password-protected.

All logbooks, integrated screening, consent and questionnaire forms, and patient registers will be securely stored as described above until data entry, cleaning, and analysis is complete; at that point all hard copies will be destroyed. All reports and manuscripts will include only de-identified and aggregated data. Potentially identifiable data will not be shared with anyone outside of the evaluation team.

8.4 Benefits

The benefits of this study include strengthening the services provided to mothers and infants as part of Malawi's Integrated ART/PMTCT Program. In addition, mothers of unknown HIV status or with an HIV-negative test result older than 3-months will have the opportunity to learn their HIV status and be linked to appropriate HIV prevention and treatment services. Mothers and infants will not receive any direct compensation for their study participation.

In addition, by implementing VL testing on mothers, this study will serve to support Malawi in scaling-up VL testing as per the National Lab Strategy and HIV Clinical Guidelines. The subgroup of mother-infant pairs consenting to be followed for 48 months may benefit from extended and enhanced monitoring, care and support.

8.5 Risks

Investigators believe that this study poses no more than minimal risk to study participants. Mothers may experience some distress or discomfort while answering questions during the interview process; they are able to withdraw from the study at any time or refuse to respond to certain questions and interviewers will be trained to provide support to these women.

The process of blood collection for either DBS or rapid HIV testing of the child may cause some discomfort/ risk but standard aseptic procedures will be followed and investigators believe the risk to be minimal.

Mothers who receive an HIV diagnosis for themselves and/or their infants may also experience emotional distress. All mothers will be provided with post-test counseling by a trained counselor.

8.6 Ethical Approval for the Study

Ethical approval for this study has been obtained from the National Health Science and Research Committee (NHSRC), the local IRB in Malawi, and is pending from "human subjects (CDC not engaged)" approval will be obtained from the Division of Global HIV/AIDS at the US Centers for Disease Control and Prevention. (See attached letters). CDC-Malawi COP funding will be utilized for this study, and implemented by MSH (with the support of Dignitas International), an implementing partner of CDC-Malawi. This is reflected in the PI and co-investigators list.

9. Handling of Unexpected Events

9.1 Response to unexpected findings and changes in study environment

The study team including members from CDC Malawi, CDC Atlanta, and MOH will meet regularly throughout the study to monitor progress and any unexpected issues that may arise during study implementation.

9.2 Identifying, managing and reporting adverse events

Potential adverse events would most likely to be related to a positive HIV test result and subsequent emotional distress. All clinic staff and the study-specific lay workers will have received training in HIV counseling and testing, and will be able to provide support for the mother and infant.

In addition, there is a small risk of infection or minor bleeding related to collecting blood from either the mother or infant.

10. Anticipated products or interventions

This study will test the feasibility of a modification of a methodology suggested by Rollins et al (Ref) for surveillance of national PMTCT programmes. If feasible, this approach may be repeated in the future producing valuable strategic information for PMTCT program management and may be shared with other countries.

11. Dissemination and Reporting of Results

A final report will be made to the MOH, all stakeholders including the relevant national TWGs, the National AIDS Commission (NAC), the Office of the President and Cabinet (OPC), UNAIDS, UNICEF, WHO, and key implementing partners in country. Publication in a peer-reviewed journal or presentations at national or international meetings or conferences will be subject to approval by relevant national authorities, and will be undertaken at least semi-annually for the duration of the study.

12. Study Timeline

	Month of study																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18-24	25-30	31-36	37-42	43-48	49-54
Finalization of protocol/tools	X	X																					
Development of electronic data entry		X	X	X																			
Pilot study		X	X																				
Revision of tools/data entry system			X	X																			
Selection of lay workers/ supervisors		X	X	X																			
Training of study/ program staff			X	X												X			X		X		
Data collection/ entry					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Data cleaning and analysis							X			X			X			X		X	X	X	X	X	X
Report writing								X			X			X			X	X	X	X	X	X	X

Table 3. Time Frame for the Study

Conflicts of Interest

None

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NEMAPP Protocol Appendices

NEMAPP Appendix 1. List of Study Sites (Amended)

This is a list of study sites based on the sampling strategy described. These sites have been approved by the Ministry of Health.

Strata		Number of Sites	Total number of exposed infants in selected districts	Sample Size per site <12mos	Sample Size per site <12wks	Number of Sites for annual 48 Mo FU	Number of Sites for quarterly 48 Mo FU
1	N/CW/CE	20	3,942	46	20	3	1
2	Lilongwe	13	4,008	63	30	3	1
3	SW/SE	22	13,395	42	18	4	2
4	Blantyre	13	4,786	55	20	3	1

Site Number	Strata	District	Facility Name	sample size per site <12mos/age	sample needed per site <12wks/age	Extra sites in order of selection	Extended annual 48 Month Follow up	Extended quarterly 48 Month Follow up
1	1	Dedza	Mua Mission Hospital	46	20			
2	1	Dedza	Mtendere Health Centre	46	20			
3	1	Dedza	Golomoti Health Centre	46	20			
4	1	Dedza	Dedza District Hospital (x6)	276	120	1, 4	276	276
5	1	Mzimba South	Katete Community Hospital	46	20			
6	1	Mzimba South	Embangweni Mission Hospital	46	20	3		
7	1	Mzimba South	Mzimba District Hospital	46	20		46	
8	1	Mzimba South	Mzambazi Community Hospital	46	20	5		
9	1	Nkhata Bay	Kachere Health Centre	46	20			
10	1	Nkhata Bay	Chintheche Rural Hospital	46	20			
11	1	Nkhotakota	Dwambazi Rural Hospital	46	20	2		
12	1	Nkhotakota	Alinafe Community Hospital	46	20			
13	1	Nkhotakota	Nkhunga Health Centre	46	20			
14	1	Nkhotakota	Nkhotakota District Hospital	46	20		46	
			Total Strata 1	**874**	**380**		**368**	**276**

Site Number	Strata	District	Facility Name	sample size per site <12mos/age	sample needed per site <12wks/age	Extra sites in order of selection	Extended annual 48 Month Follow up	Extended quarterly 48 Month Follow up
15	2	Lilongwe	Mbabvi Health Centre	63	30			
16	2	Lilongwe	Kabudula Rural Hospital	63	30			
17	2	Lilongwe	Nathenje Health Centre	63	30			
18	2	Lilongwe	Chitedze Health Centre	63	30	1		
19	2	Lilongwe	Kamuzu Central Hospital Opd1	63	30			
20	2	Lilongwe	St Gabriel Mission Hospital	63	30	2, 4		
21	2	Lilongwe	Likuni Mission Hospital	63	30		63	
22	2	Lilongwe	Area 18 Health Centre	63	30	5		
23	2	Lilongwe	Area 25 Health Centre (x3)	189	90	3	189	189
24	2	Lilongwe	Kawale Health Centre (x3)	189	90		189	
			Total Strata 2	**882**	**420**		**441**	**189**

25	3	Chikwawa	Mapelera Health Centre	42	18			
26	3	Chikwawa	St Montfort Hospital	42	18			
27	3	Chikwawa	Ngabu Rural Hospital	42	18	3		
28	3	Machinga	Machinga Health Centre	42	18	5		
29	3	Machinga	Mangamba Health Centre	42	18			
30	3	Machinga	Namanja Health Centre	42	18			
31	3	Machinga	Nsanama Health Centre	42	18			
32	3	Machinga	Machinga District Hospital	42	18	2	42	42
33	3	Thyolo	Satemwa Clinic	42	18			
34	3	Thyolo	St Martins Molere Health Centre	42	18			
35	3	Thyolo	Thunga Health Centre	42	18			
36	3	Thyolo	Mangunda Health Centre	42	18			
37	3	Thyolo	Thekerani Health Centre	42	18			
38	3	Thyolo	Bvumbwe Research H Centre	42	18			
39	3	Thyolo	Thyolo District Hospital	42	18		42	
40	3	Zomba	Naisi Health Centre	42	18			
41	3	Zomba	Namikango Health Centre	42	18	1		
42	3	Zomba	Domasi Rural Hospital	42	18			
43	3	Zomba	St Lukes Mission Hospital	42	18	4	42	
44	3	Zomba	Likangala Health Centre	42	18			
45	3	Zomba	Mativa Health Centre	42	18			
46	3	Zomba	Zomba Central Hospital Tisungane	42	18		42	42
			Total Strata 3	**929**	**399**		**168**	**84**

47	4	Blantyre	Madziabango Health Centre	55	20			
48	4	Blantyre	Lirangwe Health Centre	55	20			
49	4	Blantyre	Mlambe Mission Hospital	55	20	3		
50	4	Blantyre	Chileka Health Centre Blantyre	55	20			
51	4	Blantyre	South Lunzu Health Centre	55	20			
52	4	Blantyre	Chilomoni Health Centre (2x)	55	40		110	110
53	4	Blantyre	Bangwe Health Centre	55	20	2		
54	4	Blantyre	Zingwangwa Health Centre (2x)	110	40	5	110	
55	4	Blantyre	Ndirande Health Centre (3X)	165	60	1, 4	165	
			Total Strata 4	**715**	**260**		**385**	**110**
			TOTALS	**3400**	**1459**		**1362**	**659**

NEMAPP Appendix 2. Sample Size Calculations

MTCT rates vary according to the duration of mother's ART and subsequent viral suppression while the child is exposed: the sample size calculations take into account programmatic data for the categories of ART since before pregnancy, ART during pregnancy, ART started while breastfeeding, and No ART. The estimated MTCT rates for each regimen at two time points are based on when the mother initiated ART. The overall estimated rates are based on the known distribution of the regimen and the estimated transmission rate.

	Population Denominator (not Program)							PMTCT Cascade Coverage							
	New ANC Reg. per year	ANC Prev. Prog Data 2012	Prevalence adjusted for 80% sensitivity in ANC	% ANC attend-ance	Est HIV-infected women per year	Est HIV-exposed deliv-eries per year (97% alive)	% ANC HIV test	No ARVs in Pregnancy (Population + Program)		ART in ANC		ART before preg		ART during preg	
								N	%	N	%	N	%	N	%
National	640,576	8.4%	10.4%	97%	66,880	64,874	77%	34,062	50.9%	32,818	50.6%	11,790	36%	21,028	64%
Strata															
North, Central W & E Rural	245,378	5.0%	6.3%	97%	15,428	14,965	72%	7,736	50.1%	7,692	51.4%	3,808	39%	3,884	61%
Lilongwe	86,634	6.2%	7.8%	97%	6,725	6,523	83%	2,583	38.4%	4,142	63.5%	1,572	30%	2,570	70%
South W & E Rural	267,028	11.3%	14.1%	97%	37,684	36,554	77%	18,586	49.3%	19,098	52.2%	7,532	36%	11,566	64%
Blantyre	41,536	10.9%	13.6%	97%	5,649	5,479	75%	1,453	25.7%	4,196	76.6%	2,080	37%	2,116	63%
	640,576				65,486	63,522				35,128		14,992		20,136	

Continued from previous page

	Estimated transmission rates						Using OpenEpi exact confidence intervals for a proportion									
	MTCT at 4-12 weeks		MTCT at 12 mos*		MTCT at 24 mos		Varied precision	Design Effect	Effective sample size at 4-12wks	Effective sample size at 24mos	Lost to follow-up at 24 mos	Final Sample Size needed for 4-12 wk MTCT	Final Sample Size needed for 24mo MTCT	Final Sample Size needed for 4-12 wk MTCT	Final Sample Size needed for 24mo MTCT	Number of infants to be screened in <5 clinic in order to reach sample size
	N	%	N	%	N	%								Strata increased proportionally to reach national		
National	8,453	13.0%	12,377	19.1%	17,291	26.7%	2.5%	2.0	1,376	2,363	30%	1,448	3,376			
Strata																
orth, Central W & E Rural	1,895	12.7%	2,788	18.6%	3,904	26.1%	5.0%	1.5	253	436	30%	266	623	399	917	**14,585**
Lilongwe	687	10.5%	1,048	16.1%	1,494	22.9%	5.0%	1.5	250	391	30%	263	559	394	822	**10,594**
South W & E Rural	4,627	12.7%	6,809	18.6%	9,537	26.1%	5.0%	1.5	253	441	30%	266	630	399	928	**6,572**
Blantyre	425	7.8%	697	12.7%	1,025	18.7%	5.0%	1.5	163	337	30%	172	481	257	709	**5,212**
	7,634	12.0%	11,342	17.9%	15,960	25.1%			**919**	**1,605**		**967**	**2,293**	**1,448**	**3,376**	**36,963**

**MTCT at 12 mos assumes 50% of non-PMTCT mothers are identified in under-5, enrolled and retained at 12mos, and 80% of previously enrolled mother-infant pairs*

NEMAPP Appendix 3. Description 48 Months Extended Follow Up

Summary: The **48 months extended cohort** will allow the study team to follow a subset of 1,324 mother-infant pairs annually to 48 month post-partum to determine survival, standardized ART outcomes, and enhanced clinical outcomes (including blood sampling for CD4, viral load and hepatitis screening/disease specific markers). In **a smaller subset of 500 mother-infant pairs (out of the 1,324), enhanced follow up** for more detailed description of morbidity, growth, adverse effects and drug toxicity, recurrent pregnancies and family planning utilization will be done through quarterly study visits.

Objectives:

1. Estimate long-term survival at 12, 24, 36 and 48 months for mother-infant pairs initiated on ART under Option B Plus and describe maternal and infant characteristics associated with mortality.
2. Measure rates of long-term retention in ART for HIV-infected mothers and their infants to 48 months (alive on ART, defaulted, stop ART, transferred; including intercurrent changes of the defaulted and stop ART status)
3a. Estimate long-term ART adherence via routinely collected data (pill counts, missed pill self-reports and missed/delayed visits from standard maternal ART cards) and enhanced study visit screening (via quarterly questionnaire)
3b. Estimate long-term adherence and ART failure by viral load measurement collected at 6, 12, 24, 36 and 48 months post ART initiation. Describe the maternal characteristics that are associated with non-adherence and ART failure.
4. Describe immunological and clinical outcomes among mother-infant pairs, including co-morbid conditions, hospitalizations, opportunistic infections (including TB screening/case finding) and biometric measurements (growth, BMI) at quarterly study visits. Describe the associations of clinical outcomes with maternal and infant characteristics
5. Study the effects of TDF/3TC in hepatitis B virus co-infected patients through annual serological sampling
6. Evaluate the safety of ART within the Option B Plus strategy, including rates of drug toxicities (which will include an annual blood sample for creatinine and a urine sample), ARV regimen changes, and occurrence of birth defects through interviews at quarterly study visits
7. Evaluate subsequent pregnancies, including the incidence and interval of recurrent pregnancies, ANC service uptake in recurrent pregnancies, pregnancy outcomes and early HIV-transmission
8. Describe resistance patterns among women with HIV-1 RNA >400 copies/ml and study factors associated with drug resistance
9. Describe the preferences, uptake and use of family planning after the incident birth.

Expected Outcomes:

1. Survival rates of mothers and infants at 36 and 48 months, determined by Kaplan-Meier survival analysis and assessment of risk factors for mortality determined by Cox regression analysis.
2. Rates of defaulting, transfers to other clinic and stop ART determined by Kaplan-Meier survival analysis and assessment of risk factors for defaulting determined by Cox regression analysis.
3. Rates of non-adherence as measured by pill counts, self-report, missed/delayed clinic visits and HIV-1RNA and rate of virological failure determined by Kaplan-Meier survival analysis and assessment of risk factors for non-adherence and virological failure determined by Cox regression analysis. Description of resistance patterns in those with virological failure.
4. Description of health status (self-reported and functional), morbidities, hospitalizations, growth of infants, side effects (including lipdystrophy, renal function and cardiovascular profile), HCV prevalence, HBV prevalence and HBV treatment outcomes in those infected, utilization of family planning and recurrent pregnancies and outcomes thereof.

Methods:

Please note for full methods see main body of the research protocol. The following description pertains only to the additional procedures for the 48 month cohort.

Sample size

The sample size of the subset of the mother-infant pair cohort that will be followed for 48 months is based on the viral suppression rate amongst mothers of enrolled infants. Given that no data exist for viral suppression rates at 48 months in similar circumstances, we chose 50% based on estimated annual losses of viral suppression of 5-10% and similar percentages of losses to follow up. Using Open-Epi Exact Confidence Intervals for a proportion with the same requirements as stated in the sample size calculation for the general cohort, we estimate that 1,324 mothers will need to be enrolled into the extended follow-up study cohort to arrive at a national estimate of viral suppression with 5% precision and a 95% confidence interval.

A smaller subset of 500 mother-child dyads will be selected from the above cohort for quarterly enhanced follow up. This will allow estimation of the occurrence of adverse outcomes (a composite of side effects and morbidities, expected to be around 30% annually) with 5% precision and a 95% confidence interval.

Site selection

We selected 13 sites by PPS from the 4 geographical strata. Each site was among the selected sites for the general study, had to have a comparable expected number of exposed infants and the expected number of exposed infants of the 13 sites had to be

large enough to make up the required sample size of 1,324. For the subset of 500 women to be enrolled in enhanced followup (quarterly visits), five sites from across all geographical strata have been selected purposefully from the 13 sites described above.

Study Procedures

All main study procedures have been outlined in the main body of this study. See Methods Section. This includes data management, ethical issues (including specific consenting procedures for enrollment and follow-up within this 48-month extended cohort). See Appendices for study consent forms.

Data collection

In this subset, the following data will be collected in addition to the main study data collection procedures:

I. All **1,324 mother-child pairs will have annual study visits from enrollment to 48 months that** will include the following:

- For all **mothers**:
  - Determination of survival, standardized ART outcomes and routine adherence data from ART master cards
  - Administration of an annual questionnaire (See appendices "Annual Questionnaire Form" which is the same as per the main cohort)
  - Administration of an annual measures form which includes weight, height, hip to waist ratio and blood pressure (See appendices "Annual Measures Form")
  - Annual blood sampling for HIV-1 RNA
    - In those with HIV-1 RNA >400, genotypic resistance assays will be done
  - Annual CD4
  - Baseline Hep B and C screening
    - In those who are hepatitis B infected at baseline (expected 5-10%), HBV-DNA, HBeAg and HBsAg will be determined annually from the same sample as the HIV-1 RNA
  - Annual lipid and blood glucose monitoring for cardiovascular risk monitoring

- For all **infants** in the study
  - Determination of survival, standardized ART outcomes and routine adherence data from ART master cards

- A subsection of the annual interview form is dedicated to infant outcomes (see Appendices "Annual Questionnaire")
- Administration of an annual measures form which includes weight, height and MUAC
- Annual HIV testing as per protocol (see main study) until cessation of breastfeeding and/or documented seroconversion

II. In a subset of 500 mothers-infant pairs, in addition to the above annual procedures all dyads will have additional quarterly visits including:

- **For all mothers**:
  - Determination of survival, standardized ART outcomes and routine adherence data from ART master cards
  - A quarterly administered questionnaire that will obtain information about intercurrent morbidities (including tuberculosis and WHO stage III and IV conditions), hospitalizations, recurrent pregnancies and outcomes, and the use of family planning (See Appendices 48month extended cohort questionnaire)
  - A quarterly clinical symptoms screen questionnaire for side effects, co-morbidities and adverse outcomes
  - An annual lipodystrophy screening (see Appendices "Lipodystrophy Screen").
  - Annual blood sample for creatinine and annual urine sample
- **For all infants:**
  - Determination of survival, standardized ART outcomes and routine adherence data from ART master cards
  - A sub-section of the quarterly interview form is dedicated to infant health status and clinical outcomes

Additional appendices available upon request:

- ANC Register (MOH)
- ART Register (MOH)
- Adult ART Card (MOH)
- Pediatric ART Card (MOH)
- HIV-Exposed Infant Follow-up Card (MOH)
- ART Quarterly Reporting Forms (MOH)
- Study Cohort Register
- Testing logbook
- 48-month Follow-up Register
- Site Supervision Form
- Community Tracer logbook
- Community Tracing Form

Curriculum Vitae

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EDUCATION

Doctor of Public Health (DrPH) (expected 2017)
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Epidemiology
Completed all PhD coursework and training in Epidemiology in addition to DrPH requirements

Masters of Public Health (MPH), 2010
University of North Carolina; Chapel Hill, NC
Health Behavior & Health Education
Certificate in International Development

Bachelor of Arts (BA), 2006
St. Olaf College; Northfield, MN
History, Spanish, French
Graduated Magna cum laude

EXPERIENCE

Senior Epidemiologist and Lead for Data Use & Impact, US President's Emergency Plan for AIDS Relief (PEPFAR) / Office of the Global AIDS Coordinator (OGAC), State Department; Washington, DC (Oct 2016 – present)

- Serve as lead for data use and impact in PEPFAR, directly supervising team of five strategic information advisors (epidemiologists)
- Lead development of targets for PEPFAR's fiscal year 2017 country operational plan (COP) cycle for 37 countries at the national, sub-national, implementing partner, and facility-levels. Includes development of methodology for target-setting and development of database- and Excel-based tools to assist country teams in consultation with epidemiologists and data experts from the Centers for Disease Control & Prevention (CDC), the US Agency for International Development (USAID), the Department of Defense (DOD), and other U.S. Government Federal Agencies.
- Serve as strategic information advisor and primary liaison between the Office of the Global AIDS Coordinator (OGAC) and Mozambique & Côte d'Ivoire country programs for all data and epidemiology-related program issues
- Develop PEPFAR guidance on data collection, indicator definitions, data analysis, and use; regularly contribute to design of data visualizations for internal and external PEPFAR websites
- Lead development of all major presentations for U.S. Global AIDS Coordinator (2-4 presentations/week) for scientific and non-scientific audiences.

Senior Advisor, US President's Emergency Plan for AIDS Relief (PEPFAR) / Office of the Global AIDS Coordinator, State Department; Washington, DC
Detailed from the Centers for Disease Control & Prevention (CDC) to State Department (Aug 2014 – Oct 2016)

- Served as senior advisor for epidemiology, data analysis, and data visualization, for the U.S. Global AIDS Coordinator and U.S. Special Representative for Global Health Diplomacy, who oversees the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the U.S. contribution to the Global Fund for AIDS, Tuberculosis, and Malaria, with a total annual budget of $6.8 billion in fiscal year 2016.
- Continuously reviewed PEPFAR program data and independently conducting epidemiological analyses to inform PEPFAR programmatic direction and policy priorities.
- Provided scientific leadership on PEPFAR technical guidance and strategy documents
- Led development of all major presentations for the U.S. Global AIDS Coordinator (2-4 presentations/week) for scientific and non-scientific audiences

Senior Advisor for Prevention of Mother-To-Child Transmission of HIV (PMTCT), US President's Emergency Plan for AIDS Relief (PEPFAR)/Office of the Global AIDS Coordinator, State Department; Washington, DC
Detailed from the Centers for Disease Control & Prevention (CDC) to State Department (Jul 2011-Aug 2014)

- Managed PEPFAR's work in maternal & child health and virtual elimination of new pediatric HIV infections
- Oversaw portfolio with $300 million annual budget to support PMTCT programs in 27 countries
- Provided technical leadership as co-chair of PEPFAR PMTCT & Pediatrics Technical Working Group
- Represented US government on Executive Committee of Inter-Agency Task Team (IATT) on PMTCT; technical collaboration with >30 partners (multilateral, bilateral, public, private, NGO, and civil society)
- Conducted regular technical assistance visits to support programs in Sub-Saharan Africa (8-12 visits/year)
- Advised senior leadership (US Ambassadors, Ministers of Health, National AIDS Control Directors) and provided technical and management recommendations for PEPFAR and national HIV/AIDS programs
- Developed and contributed to presentations, speeches, blogs, and opinion pieces for senior US government officials (including Ambassador, Secretary of State, President)

Public Health Analyst, Centers for Disease Control & Prevention (CDC), Global AIDS Program; Atlanta, GA
Senior Program Manager, Office of the Director, Division of Global HIV/AIDS (Mar-Jul 2011)

- Provided direct programmatic, management, and advisory support to Director of CDC's Division of Global HIV/AIDS (DGHA), who oversaw an annual budget of nearly $2 billion and >3,000 staff
- Developed internal & external communications on behalf of Division Director; drafted presentations and speeches; represented the Division in high level CDC management meetings

- Managed high priority initiatives across the Division including development of Country Management & Support strategy to enhance oversight and accountability across 43 country programs

Country Officer, Country Operations Branch (Jul 2010-Feb 2011)

- Served as liaison between CDC headquarters and field offices in six countries (Afghanistan, Cameroon, Haiti, Nigeria, Pakistan, and [South] Sudan);
- Provided technical and operational support to country teams via regular technical assistance visits
- Managed Division-wide Country Assistance Plan review process
- Coordinated interagency Country Operational Planning process in Cameroon including development of $15M budget

Sexual & Reproductive Health Capstone, El Pueblo; Raleigh, NC / Ipas; Chapel Hill, NC (Aug 2009-May 2010)

- Designed and conducted evaluation of comprehensive sexual and reproductive health program to train Latino youth in advocacy and peer education
- Conducted in-depth interviews and focus group discussions with 20 recently-trained Latino youth and their parents; presented findings to funders
- Developed 300-page evidence-based curriculum incorporating evaluation results

Water and Environmental Sanitation Intern, UNICEF; Dhaka, Bangladesh (May-Jul 2009)

- Conducted critical analysis of external health impact study of UNICEF's Sanitation, Hygiene Education, and Water Supply in Bangladesh program, which reaches over 32 million people
- Developed monitoring and evaluation framework and conducted site visits in rural regions
- Contributed to national disaster preparedness plan; reviewed relief proposals from international NGOs after Cyclone Aila; coordinated relief plan with senior government officials

Graduate Research Assistant, UNC Lineberger Cancer Center; Chapel Hill, NC (Aug 2008-May 2009)

- Conducted literature reviews on disparities in access to cancer screening among minority populations
- Developed IRB proposal and contributed to qualitative study with 300 low-income and minority residents regarding access to cancer screening and treatment services in North Carolina
- Designed Capstone project for MPH students with United Way to improve 2-1-1 hotline for social services

Analyst, Technology and Management Services, Inc.; Washington, DC
U.S. Department of Energy – Energy Efficiency and Renewable Energy (EERE) (Jul 2006-Jun 2008)

- Managed EERE's clean energy work with National Governor's Association; liaised with senior state policy advisors to coordinate federal and state energy priorities
- Developed metrics to evaluate state investments in clean energy

- Synthesized information into briefing documents and regularly briefed senior Department officials
- Drafted speeches and managed Congressional correspondence

U.S. Bureau of Indian Affairs (Sep-Dec 2006)
- Researched American Indian education; conducted literature review; assisted in design of evaluation and interview guide for key informant interviews and focus groups; contributed to final research report

West Africa Intern, American Refugee Committee, International (ARC); Minneapolis, MN (Feb-May 2006)
- Supported Director of African Programs; drafted grant proposals for gender-based violence, reproductive health, HIV/AIDS, and microenterprise development projects in West Africa

Oral History Research & Volunteer, Children Better Way (CBW); Bududuram Refugee Camp (Jan 2006)
- Awarded competitive Kloeck-Jensen Grant for Peace and Social Justice from St. Olaf College to conduct oral history research in Liberian refugee camp in Ghana
- Recorded personal stories of 22 refugees regarding Liberian Civil War and extended exile in the Bududuram Camp; developed senior thesis for history degree based on this primary research
- Volunteered with local community-based organization, Children Better Way: taught French classes, assisted in HIV/AIDS outreach, developed curriculum for adult literacy program, led after school recreational activities

AWARDS & HONORS

Extra Mile Award, US Department of State

Selected for Department-wide award for outstanding performance and technical assistance provided to the President's Emergency Plan for AIDS Relief (PEPFAR) country teams in strategically analyzing and using data to help achieve HIV/AIDS epidemic control (2017)

HIV/AIDS Training Grant, National Institutes of Health (NIH) and Johns Hopkins University Bloomberg School of Public Health

Selected for highly competitive pre-doctoral training position on the HIV Epidemiology and Prevention Sciences Training Program at Johns Hopkins Bloomberg School of Public Health. Training grant includes full tuition for doctoral studies, stipend, and support for research-related expenses (2016-2017)

Mary B. Meyer Fellowship, Epidemiology Department, Johns Hopkins University Bloomberg School of Public Health

Selected for highly competitive fellowship including full tuition for doctoral studies and stipend (2014-2016)

Center for Global Health (CGH) Director's Medal of Excellence in Global Health, CDC
Selected for demonstrating exemplary service within CDC's Center for Global Health by exemplifying high ideals, innovation, and impact in the context of global HIV/AIDS (2012)

Commitment Award, US Department of State, Office of the Global AIDS Coordinator, State Department
Twice recognized for demonstrating the highest level of commitment to public health service through advancing PMTCT and pediatric HIV programming in PEPFAR (2012, 2013)

CGH Director's Hardship & Difficult Circumstances Award, Centers for Disease Control & Prevention (CDC)
Recognized for working under very difficult circumstances for program development in South Sudan and overall support of CDC's Center for Global Health international public health programs (2011)

Complex Humanitarian Emergency Training Program, US Centers for Disease Control and Prevention (CDC)
Selected for competitive 2-year professional training program; includes 4 weeks of coursework and mentored field experience in international emergency response; co-led first Knowledge, Attitudes, and Practices (KAP) Assessment in Artibonite region of Haiti after cholera outbreak; trained and supervised 22 Haitian enumerators; collected data via 512 household surveys and 7 focus groups (Oct 2010-2012)

Presidential Management Fellow (PMF), US Federal Government
Selected for highly competitive US federal government leadership program; two-year fellowship included full-time employment at CDC, 160 hours of formal classroom training, several rotations within CDC and to State Department, and accelerated promotion (Jul 2010-Jul 2012)

Arabic Foreign Language and Area Studies (FLAS) Fellowship, US Dept. of Education
Awarded full tuition and stipend for second year of masters of public health program including support for continued study of Arabic language (Aug 2009 – May 2010)

Arabic Fellow, State Department National Security Language Initiative; Tunis, Tunisia & Salalah, Oman
Twice awarded highly competitive Critical Language Scholarship for intensive summer study of Arabic in Tunisia (Beginning Arabic) and the Sultanate of Oman (Intermediate Arabic) (May-Jul 2007; Jun-Aug 2008)

PUBLICATIONS & PRESENTATIONS

Radin AK, Abutu AA, Okwero MA, Adler MR, Anyaike C, Asiimwe HT, Behumbiize P, Efuntoye TA, King RL, Kisaakye LN, Ogundehin DT, Phelps BR, Watts H, and Weissglas F. Confronting challenges in monitoring and evaluation: Innovation in the context of the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their

mothers alive. *Journal of Acquired Immune Deficiency Syndrome (JAIDS)*. 2017, May 1; 75(s1): s66-s75.

Radin AK, Stover J. Reviewing PMTCT Coverage: Analysis of Spectrum model inputs that affect national and sub-national PMTCT coverage estimates. Oral presentation at: Annual Meeting of the UNAIDS Reference Group on Modeling, Estimates, and Projections: Method Development for the UNAIDS Estimates; New York, NY, 2016.

Radin AK, Stover J. Analysis of Spectrum model for PMTCT coverage estimates and Implications for Children. Oral presentation at: UNAIDS, UNICEF, and WHO Meeting on Estimating the Future of Paediatric HIV and the Need for ART; New York, NY, 2016.

Chimbwandira F, Mhango E, Makombe S, Midiani D, Mwansambo D, Njala J, Chirwa Z, Jahn A, Schouten S, Phelps BR, **Gieselman A**, Holmes CB, et al. Impact of an innovative approach to prevent mother-to-child transmission of HIV--Malawi, July 2011-September 2012. *CDC MMWR Morbidity & Mortality Weekly Report.* 2013 Mar 1;62(8):148-51.

Adler MR, **Gieselman A**. Moving to B/B+: Readiness Assessment Checklist and Discussion Guide for National Programs. In Inter-Agency Task Team on the Prevention and Treatment of HIV in Pregnant Women, Mothers, and Children ed. *Option B+ Toolkit: Expanding and Simplifying Treatment for Pregnant Women Living with HIV.* 2012. Available at: http://www.emtct-iatt.org/toolkit/. Accessibility verified September 6, 2016.

Chi BH, Adler MR, Bolu O, Mbori-Ngacha D, Ekouevi DK, **Gieselman A**, Chipato T, Luo C, Phelps BR, McClure C, Mofenson LM, Stringer JS. Progress, challenges, and new opportunities for the prevention of mother-to-child transmission of HIV under the US President's Emergency Plan for AIDS Relief. *Journal of Acquired Immune Deficiency Syndrome.* 2012 Aug 15: 60 Suppl 3:S78-87

Jacobson L, **Gieselman A**, Gaines J, Blanton C, McCormick E, Barbour K, Hyppolite C, Roodly Archer W, Roels T, Tappero J, Handzel T. Knowledge, Attitudes, and Practices Related to Cholera Prevention and Treatment — Artibonite Department, Haiti, 2010. Poster presented at: Epidemic Intelligence Service Conference; Atlanta, GA, 2011.

Gaines J, **Gieselman A**, Jacobson L, Demas S, Person B, Roels T, Tappero J, Quick R, Handzel T. Life Inside an Outbreak: A Qualitative Assessment of Cholera Response Efforts, Artibonite Department, Haiti, 2010. Poster presented at: Epidemic Intelligence Service Conference; Atlanta, GA, 2011.

LANGUAGE SKILLS

English: Native speaker
French: Advanced professional proficiency
Spanish: Advanced professional proficiency
Modern Standard Arabic: conversational proficiency